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Report from SSM's scientific council on ionizing radiation within oncology, 2013

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SSM perspective

Background

In 2009, the Swedish Radiation Safety Authority (Strålsäkerhetsmyndigheten, SSM) appointed a scientific council on ionizing radiation within oncology. The council consists of scientific experts in the fields of oncology, radiology and medical physics. Their task is to annually review and evaluate scientific developments in radiotherapy and to give SSM advice in issues where a scientific examination of different views is necessary. The council began its work in the autumn of 2009 and this is the fifth report presented.

Objectives

The council summarizes the recent scientific knowledge in the field of radiotherapy in an annual report.

Results

Imaging is important for radiotherapy and the development of new imaging modalities is closely linked to the evolution of modern radiotherapy. The implementation of magnetic resonance imaging (MRI) in modern radiotherapy holds great promise for the future but the scientific council emphasizes that it must be carefully monitored in order to minimize the introduction of new risks, violating patient safety. This report describes the use of MRI in the radiotherapy process from patient selection to follow-up and discusses possibilities and difficulties related to the introduction of MRI.

The report states that many functional MR-methods are available and if the effort to bring these methods into robust and validated biomarkers is taken in the imaging community, their working potential is immense. Further, the report states that MRI is a modality assumed to improve delineation of RT target volumes and organs at risk. Even an MRI-only approach to treatment planning, using synthetic CT for dose-calculations, has been proposed in order to avoid the uncertainties associated with image co-registration. Implementation of an MRI scanner at the radiotherapy clinic calibrated with direct links to the coordinate frame of the treatment machine and with possibilities for doing imaging of the patient in the treatment position would introduce new possibilities for set-up treatment verification and adaptation of the treatment volume according to the changes in patient anatomy. The scientific council underlines that when introducing MRI in radiotherapy there are important factors that need to be taken into account, e.g. forming new multidisciplinary teams, additional education and the quality assurance.

The council believes that MRI in radiotherapy is a new and promising area of research that aims to further optimize the radiotherapy on an individual level. For exploiting the potential benefits more research is needed in conjunction with development of competence.

Project information

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This report concerns a study which has been conducted for the Swedish Radiation Safety Authority, SSM. The conclusions and viewpoints presented in the report are those of the author/authors and do not necessarily coincide with those of the SSM.

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1. Introduction

Imaging is important for radiotherapy and the development of new imaging modalities is closely linked to the evolution of modern radiotherapy. Radiological methods used in radiotherapy have mainly been x-ray based and ranges from plain radiographs over orthogonal imaging, conventional tomography to modern computerised tomography (CT). The radiological mainstay for all steps in the radiotherapy process today is CT as the latest development in the evolution of x-ray based methods (1). This evolution over the last decades forms a solid experience base for the current imaging technology used in radiotherapy. CT is still one of the most used modalities for staging and selection of patients for correct treatment protocols. CT is also the most utilised modality for anatomic description and the base for delineation of target volumes and organs at risk. The information on x-ray attenuation delivered by CT is used for treatment planning. CT based virtual simulation have replaced x-ray based simulation in clinical practice. During treatment, on board CT such as cone beam CT (CBCT) using high or low voltage x-rays is becoming a routine method for treatment verification during treatment delivery in most specialized radiotherapy departments. Finally, response evaluation after radiotherapy is commonly based on tumour size measurements where CT still is the most common method. Although CT is the base of imaging in radiotherapy today and in the nearest future, the method has shortcomings where other radiological methods fill in important gaps. Positron emission tomography (PET) adds functional information regarding tumour metabolism and magnetic resonance imaging (MRI) is superior to CT for anatomic description and also have the advantage of adding substantially more functional information about the examined tissue. PET and MRI are today important imaging modalities for radiotherapy adding information for target delineation and treatment response but is mainly used complementary to a CT based radiotherapy workflow. The information from PET and MRI is usually utilised by different image fusion methods where the PET and/or MRI images are fused to the standard dose-planning CT images.

Due to its superior ability to define soft tissue structures, MRI is today the preferred imaging modality for several anatomical locations such as the brain, the vertebral column, the abdomen and pelvis among others. This advantage versus CT, together with the possibilities functional MRI adds, makes MRI interesting for direct implementation in the radiotherapy process. MRI has the possibility to improve all steps in the radiotherapy process from patient selection to treatment follow up. Improved anatomical description using MRI improves pretreatment staging of patients and thereby also patient selection. MRI for target delineation has clearly advantages over CT in many cases

and MRI based radiotherapy workflows are to be expected in the near future. The introduction of MRI in radiotherapy have improved many steps in the radiotherapy process but also introduces new methodological uncertainties when x-ray based methods at least partly are abandoned.

The implementation of MRI in modern radiotherapy holds great promise for the future but must be carefully monitored in order to minimise the risk of introducing new risks violating patient safety.

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1.1 Personalised radiotherapy

Personalised medicine is the development of customized interventions based on individual patient characteristics. Personalised cancer treatments are today becoming more common in medical oncology partly due to the rapid development of biomarkers as predictive factors for cancer treatment. Predictive biomarkers are interesting also in radiotherapy for prediction of response and normal tissue reactions (2,3). However, personalised radiotherapy is more than predictive biomarkers and the development of imaging modalities in parallel with

the evolution of the modern linear accelerator have formed the base for individualisation of radiotherapy treatments. By abandoning fixed-field treatments and entering the era of 3D conformal radiotherapy (3DCRT), personalised radiotherapy delivery have been introduced. The development of personalised radiotherapy is closely connected to the development of new imaging modalities such as MRI. Improved imaging may contribute to personalised radiotherapy in all steps of the radiotherapy process. First, improved imaging including functional imaging may improve staging of patients and also harbours the possibilities of finding radiological predictive biomarkers for patient selection (4-6). Better anatomical description of target volumes clearly improves the individual treatment plan and better imaging may also contribute to more accurate treatment verification during treatment. Finally, improved imaging contributes to improved follow up of treatment response especially when functional imaging is introduced.

1.1.1 MRI in personalised radiotherapy

Beside better anatomical description and thereby an improved individualisation of treatments, the functional aspects of MRI adds possibilities to develop personalised radiotherapy further. Using advanced MR protocols such as dynamic contrast enhanced (DCE) MRI, MRS and diffusion weighted sequences different aspects of tumour physiology may be measured and used for target delineation, early tumour response during the treatment period as well as for post treatment response evaluation and long term follow up.

1.2 Rationale for the present report

The development of imaging technology has been one of the most important technological advances in modern radiotherapy. CT is still the basis for all imaging steps in the radiotherapy process but MRI is now rapidly being introduced. Due to the superior soft tissue discrimination MRI has gained importance in the first steps of the radiotherapy process including patient selection for treatment as well as for target delineation. The possibility of functional imaging makes MRI an interesting modality for biological dose planning, early response assessments and new follow-up protocols. Since the introduction of CT based 3DCRT, radiotherapy may be considered to have entered the era of personalised medicine. The introduction of MRI will not only have advantages in target delineation but will also make it possible to individualise radiotherapy further by using different aspects of functional imaging.

The use of MRI in radiotherapy is a rapidly developing field and radiotherapy dedicated MRI scanners are now installed in an increasing number in radiotherapy departments worldwide. The introduction of MRI in radiotherapy will most certainly contribute to improved treat-

ment possibilities but introduction of a new imaging modality also represent a challenge to the radiotherapy community. This report describes the use of MRI in the radiotherapy process from patient selection to follow-up and discusses possibilities and pitfalls related to the introduction of MRI.

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2. Anatomical and functional MR-imaging

2.1 Anatomical imaging of target and OAR volumes

Imaging that provides information about the shape and size of an organ in the body as well as the relation between different organs is usually referred to as anatomical imaging. In the initial era of diagnostic radiology, this was provided by conventional x-ray. Soon after the introduction of x-ray, functional information was obtained fluoroscopy and administration of contrast agents (1-3). Today, diagnostic imaging mainly consists of computerized cross sectional imaging modalities, which started with computerized tomography followed by ultrasonography (4) and magnetic resonance imaging (5-7).

Although all cross sectional modalities have potentials for functional imaging, the majority of their clinical use has so far been for identification of pathology in the body based on visual/ qualitative assessment of morphological changes in attenuation, echogenicity or signal intensity compared to healthy tissue. Soon after the introduction of the different imaging techniques, the possibility to detect solid tumours in the body was evaluated (8,9). Imaging was also evaluated for TNM staging of tumours (10,11).

The contrast resolution properties of cross sectional imaging techniques was also the basis for the possibility to establish tumour response assessment criteria such as the WHO-critera, RECIST and RECIST 1.1 (12,13). It has also been the basis for using CT and MRI for radiation treatment planning (14).

Today, cross sectional anatomic imaging constitute a significant proportion of the work load in diagnostic radiology departments. The continuous increase in the number of CT examinations has raised a concern for the load of ionizing irradiation to the population. The Nordic Radiation protection co-operation has thus drawn attention to the risks of irradiation and implemented a “triple-A” concept, Awareness, Appropriateness and Audit (www.stralsakerhetsmyndigheten.se).

The use of anatomical imaging is becoming more sophisticated, dissolving the border between anatomical and functional imaging. Doppler ultrasonograpy, elastography, Histoscanning®, contrast enhanced

ultrasound, multiphasic contrast enhanced CT, perfusion CT and dual energy CT are all examples of functional imaging techniques usually integrated in an anatomical imaging examination. In MRI, the number of functional techniques that can be used together with anatomical imaging are many. The term "multiparametric MRI" often refers to a combination of anatomical and functional imaging techniques used in conjunction for assessment of disease (15).

2.2 Functional imaging

As indicated above, most imaging modalities can be used for both anatomical imaging as well as functional imaging. Functional images differ from anatomical in that the contrast in the image is based on the tissue function rather than on anatomy. Traditionally, certain modalities have been classified as functional per se, i.e. modalities based on nuclear medicine, which image the bio-distribution of radioactive tracers. These images are obtained with gamma cameras (static, scanning or rotating) or PET cameras, which in combination with CT result in SPECT/CT and PET/CT. Recently, the PET camera has also been combined with MRI in an integrated PET/MR unit. Techniques based on radioactive tracers, especially PET, is the main functional imaging modality in oncology. The impact of PET on decision making in diagnostics and treatment prediction and follow-up is undisputable (16). However, this report concerns MR applications only. In addition to its possibility to provide morphological images of excellent contrast and resolution, MRI also has a number of possibilities to provide functional information. For example MR based diffusion, spectroscopy, and magnetization transfer are functional techniques based on the endogenous contrast in the tissue, while MR perfusion (except arterial spin labelling, ASL) and permeability measurements are based on exogenous contrast agents.

Historically, the concept of functional MRI was introduced as a description for the special MR technique sensitive to brain activity and abbreviated fMRI (see below). In this report functional MRI is used in a broader sense meaning all functional MR methods, abbreviated FMRI, of which one is fMRI.

2.2.1 Perfusion assessment with DCE-MRI

Dynamic Contrast Enhanced MRI (DCE-MRI) is a technique for assessing certain vascular physiological properties of a tissue. This is of special interest in cancer since tumour growth creates an environment, which often differs from normal soft tissue with respect to the vascular structure. During tumour growth new vessels are needed, i.e. angiogenesis, but the new vessels will be of different, often poor structure, having a tortuous topology and express a certain leakiness. In short, DCE-MRI can assess tumour vasculature, perfusion, blood vessel

permeability, blood volume and extravascular/extracellular volume fraction. Obviously, all these parameters will be of high interest to characterize tumour tissue.

DCE-MRI relies on an i.v. injection of a contrast agent (CA). The standard techniques use clinically available paramagnetic gadolinium (Gd) chelates. The contrast agent affects the relaxation times T1, T2 and T2*. This section concentrates on DCE-MRI which entirely is built on the T1 shortening effect of the CA. (For T2 and T2* effects see DSC-MRI). To follow the distribution of the CA, i.e. to characterize its pharmacokinetics, a dynamic T1-weighted acquisition is performed. In order to obtain quantitative data, the acquisition protocol needs to include a T1-map and a registration of the arterial input function (AIF). The AIF describes the kinetics of the CA in the blood, which is needed for modelling. Since the duration of the arterial phase is very short, high temporal resolution is necessary, which in turn sets limitations for the spatial resolution.

The most common model for analysing the time intensity curve is Kety/Tofts. The analysis results in the parameter ktrans, which represents the transfer constant from plasma space to tissue space, often referred to as permeability, the parameter extravascular-extracellular space and the permeability-surface area product. However, Kety/Tofts and similar models require information such as T1-map and AIF, which make the acquisition protocol complicated(17). Additionally, the analysis of the data requires a great deal of computing. Therefore, several semi-quantitative methods have emerged. The most applied is initial area under the curve (AUC), which basically reflects the initial dynamics of the contrast agent. The AUC often correlates to ktrans , but the physiologic definition is unclear. Still, AUC and similar techniques are used since the acquisition protocol and the analysis are simplified.

Since DCE-MRI can assess tumour blood vessel permeability, it has successfully been used in many drug studies on substances affecting tumour vascularity. Most of these studies were in preclinical models. For example, DCE-MRI was used to evaluate the acute treatment of a vascular endothelial growth factor inhibitor on a prostate tumour in a mouse model and it was possible to obtain a dose response relationship between the drug substance and the reduction of ktrans of the tumour (18).

In radiation therapy DCE-MRI can be used as a prognostic and predictive indicator of the tumour response. The vascular permeability measured prior to radiation treatment has shown to be a prognostic factor for treatment response in malignant gliomas (19). High permeability is associated with poor response or reduced survival in malig-

nant gliomas. However, in a study of patients with cervical cancer, low uptake from DCE-MRI in tumours obtained either before or during early radiation treatment indicated a high risk for treatment failure, while in patients with initially high uptake or with improving perfusion the outcome was more favourable (20). Obviously, it is important to know the permeability properties of the tumour and other tissues of interest in order to interpret the findings of DCE-MRI.

DCE-MRI has also a potential role as a method to improve target delineation. Compared with T2-weighted MR imaging, use of DCE-MRI significantly improved accuracy in prostate cancer localization (21). The tumour definition can be further improved by multi parametric evaluation of the dynamic data (22). The functional information may be used to define sub-volumes with different biological properties within the gross tumour volume. The sub-volume may have inferior perfusion, which indicates hypoxia and a need for a higher dose. Biological information on a voxel level may be used to steer the dose within the target volume, i.e. dose sculpting or dose painting (23).

DCE-MRI results in new information useful in prognosis as well as assessment of tumour and normal tissue responses to radiation. The radiation therapy DCE-MRI may play a role in treatment modality selection, target definition, and therapy individualization, although further validation studies are needed (19).

2.2.2 Perfusion MRI with DSC-MRI

Dynamic susceptibility contrast – MRI (DSC-MRI) is built on a dynamic acquisition of MR-images before and after an i.v. injection of a contrast agent, i.e. clinically available paramagnetic gadolinium (Gd) chelates. As indicated by "susceptibility", the T2* effect from the contrast agent on the tissue is the parameter of interest. The acquired data are fitted to an appropriate pharmacokinetic model. Thereby, physiological parameters relating to blood volume (BV), blood flow (BF), and mean transit time (MTT) can be extracted. The underlying theory, which enables the calculation of the perfusion parameters, is the indicator dilution theory (24).

The calculation relies on an accurate conversion of the measured MR-signal to contrast agent concentration. For DSC-MRI this is not a straightforward task. The contrast agent affects not only T2* but also T1 and T2. Additionally, T2* is also affected by other sources of susceptibility than the contrast agent, such as tissue differences, geometry and shimming. As a result, the signal is affected by vessel size. The acquisition protocol needs to be carefully designed to avoid these confounding factors in the analysis.
The signal theory developed for DSC-MRI and clinical contrast agents is derived from principles of indicator dilution theory for non-

diffusible tracers. However, the conditions for this theory are only valid for normal brain tissue with intact blood-brain barrier. In brain tumours and other tissues lacking the blood-brain barrier, the contrast agent leaks out of the vasculature. The contrast agent in the extravascular space will affect the measured signal, and the assumption for the dilution theory is not valid. As a result the measured perfusion data will be inaccurate or even non-physiologic. There are different techniques to reduce the effects of leaking contrast agent, e.g. to minimize T1 sensitivity and absolute measurement of T2*, and correct the data accordingly. It remains still to validate that the correction techniques improve the reliability of the measured blood volume and blood flow (25). However, there are studies indicating that corrected data do correlate with tumour grade, whereas, not corrected do not (25).

Since DSC-MRI assesses perfusion, a major application has been in studies of anti-angiogenic drugs, mainly for brain tumours. In a preclinical model (gliosarcorma) DSC-MRI perfusion has been shown to be a valuable tool to non-invasively evaluate morphological and functional changes in tumour vasculature in response to angiogenic therapy (26). Recently, DSC-MRI was proven to be an effective marker of the response to anti-angiogenic therapy for patients with glioblastoma (27). DSC-MRI has a potential to be a method to identifying patients who would benefit most from anti-angiogenic therapy

One application of DSC-MRI is the assessment of brain tumour grade from blood volume maps. The general assumption is that in the brain tumour, the total vasculature generally increases with grade and thereby the measured blood volume (28). By the use of a dedicated histogram analysis of the blood volume maps obtained by DSC-MRI, a diagnostically accurate and reproducible method was found to grade gliomas.

DSC-MRI measurement of perfusion prior to radiation treatment has shown to be a prognostic factor for treatment response in malignant gliomas (29). High CBV and CBF are associated with poor response or reduced survival. Similar results were found in a study by Law (30). A measurement of CBV or CBF midterm during the radiation therapy of malignant gliomas can be valuable for identifying non-responders from responders. An assessment three weeks into a six-week treatment has shown to be predicative for the outcome (31).

Despite the confounding effects of the contrast leakage, many aspects of the microenvironment of the tumour can be characterized by DSC-MRI, such as vascular architecture, morphology and function. With improved correction methods the application and reliability may increase further.

2.2.3 Diffusion MRI

The measured MR signal is sensitive to motion, including diffusion of molecules in tissues. Diffusion is random free motion due to thermal energy and the diffusion rate can be described by the diffusion coefficient D. For biological applications it is the diffusion of water, which is of interest. In tissue the diffusion of the water molecules are affected by macromolecules, cell membranes and other tissue microstructures that hinder diffusion. Therefore, since the phenomenon is not freely diffusion molecules, it is denoted apparent diffusion. Several relevant properties of tumour tissue are known to affect the diffusion, e.g. cellularity, extracellular volume fraction, membrane permeability and tortuosity. Compared to normal tissues tumours have lower ADC (apparent diffusion coefficient) due to the increased cellularity and decreased extracellular volume fraction.

Diffusion weighted MRI is a technique in which the signal intensity in the image is dependent on the diffusion. The sensitivity of the pulse sequence to diffusion can be regulated by diffusion gradients. During the encoding of the signal a strong gradient is applied and as a result the spins dephase. If the same gradient is applied, after a short delay, with the opposite sign, the spins will rephase again if they are stationary. Spins that have moved due to diffusion will not rephase completely since they have experienced a slightly different gradient strength during the two gradient pulses. As a result, regions with high diffusion have less signal in the diffusion weighted MR-image.

The diffusion can also be quantitatively determined. If at least two diffusion-weighted images are obtained with different diffusion weighting, often referred to as b-values, the ADC can be calculated and presented as an ADC-map. The ADC-map will only show the diffusion along the direction of the applied sensitizing gradient. In order to get a map for isotropic diffusion a diffusion measurement needs to be performed along three orthogonal directions.

A special feature of MRI diffusion is diffusion tensor imaging (DTI) of the central nervous system. The effect from the diffusion on the signal is specific for the direction of the applied diffusion gradient. The ADC map may look very different dependent upon the orientation of the gradient, a result of anisotropic diffusion, i.e. that the diffusion is higher in certain directions. The degree of anisotropic diffusion is described by the fractional anisotropy[1] (FA)[1]. The dominating motion of the water molecules is along the axonal fibres. By a system of dedicated diffusion gradient directions, minimum six but often up to sev-

[1] FA=0 means that diffusion is isotropic. FA=1 means that diffusion occurs only along one axis.

eral tens, the fibre orientation can be revealed, resulting in color-coded diffusion tensor maps of the brain.

Measurement of ADC has been applied in studies to address treatment response mainly in the brain. Compared to normal tissues tumours have initially lower ADC due to the increased cellularity and decreased extracellular volume fraction. A significant increase of the ADC value was found in tumours as early as one week after the start of treatment and well before any changes in tumour size (32). There is also indication that ADC can be used for tissue characterization, and to differentiate malign from benign tumours, e.g. ADC was found to be lower in breast cancer (33). Another area of interest is ADC measurement as technique for prediction of outcome by using ADC classification of the response of brain tumours three weeks after the start of radiation treatment, which was two months earlier than standard radiological methods (34).

Recently, MRI diffusion was used to study treatment response during radiation therapy of prostate cancer (35). The ADC within tumour tissue was significantly increased already one week after the start of treatment and continued to rise until the completion of therapy one month later. The prostate specific antigen (PSA) level was not significantly different until three weeks after start of treatment. An increase in the ADC reflects increased water mobility through the loss of membrane integrity or an increase in the proportion of total extracellular fluid due to a decrease in cell size or number. The significant difference in ADC between tumour and benign tissue before radiotherapy disappeared after completion of the therapy.

Studies with DTI have demonstrated that radiation therapy decreases the fractional anisotropy of affected white matter lesions. Changes of DTI and FA have been found to correlate with radiation dose and differentiate between recurrent brain tumours and radiation injury in regions of new contrast enhancing lesions (36).

2.2.4 Magnetic resonance spectroscopy

Magnetic resonance spectroscopy (MRS) takes advantage of that spins may resonate at slightly different frequencies, if their molecular environment – chemical bonding – differ. The term chemical shift comes from the difference in resonance frequency relative to a reference compound. A well-known example is the 3.5-ppm chemical shift of fat relative water. The different compounds give rise to different peaks that together result in the MR spectrum. The area under the peak is proportional to the number of nuclei, i.e. metabolite concentration.

The spectral information does not include spatial localization per se. The spatial localization can either be obtained by using surface coils

or by the use of the gradients in the MR-scanner. The latter technique may range from single voxel spectroscopy to chemical shift imaging (CSI). CSI results in 2D/3D arrays of spectra, from which maps of the individual metabolites can be constructed. CSI is a rather time-consuming technique.

In 1H (proton) MRS, metabolites such as lactate, total creatine (phosphocreatine and creatine), and total choline (phosphocoline, glycerophosphocoline and free choline) are in general detectable as well as mobile lipids, glutamine and glutamate. The dominating signals come from water and lipid triglycerides, which therefore may need to be suppressed in order to make the metabolites distinguishable.

In 31P MRS, metabolites involved in the energy metabolism such as phosphocreatine (PCr), inorganic phosphate (Pi) and adenine triphosphate and diphosphate (ATP, ADP) can easily be detected in-vivo. The chemical shift of Pi is sensitive to pH and can be used as marker for intracellular pH (38). 19F MRS relies on that a substance containing 19F is administered, since there is no natural background signal from 19F in the body. Many drugs, including chemotherapeutic agents, contain large amount of fluorine and can be tracked by 19F MRS. 19F MRS of nitroimidazol derivatives which accumulate in hypoxic cells, has been used to obtain measurements of hypoxia (37). 13C is only 1.1% of the naturally abundant carbon. In-vivo 13C MRS is therefore impractical with endogenous metabolites, but many biological relevant molecules can be labelled with 13C for administration in preclinical models, cell studies and to some extent human studies. However, clinical applications of 13C MRS have been scarce and there has been no progress the last decade (38). The implementation of high field (>7T) clinical MR cameras may increase the possibility for 13MRS in the future. See also section on hyperpolarized 13C below.

MRS benefits from a high magnetic field strength and preclinical MRS studies (4.7- 11.7T) are therefore particularly well suitable. These studies can provide information on tumour metabolism, pH, hypoxia, drug delivery, treatment efficacy or apoptosis (37).

1H MRS can contribute to improved characterization, grading and staging of the tumour in the brain. When normal tissue is destroyed and the cancer cells are increasing, the spectral changes. There is a decrease in NAA and an appearance of lactate and lipids and decrease of total choline (37). 1H MRS has been studied as a marker for predicting survival for patients with glioblastoma. Poor outcome was related to high levels of lactate before radiotherapy (39). In breast, 1H MRS can contribute to identify the active tumour by detecting elevated choline levels. Contrast enhanced-MRI is still the major technique, but adding 1H MRS improves the specificity. Similarly, 1H MRS can

be added to CE-MRI in the protocol for monitoring treatment response of breast cancers with an expected substantial advantage in the prediction to neo-adjuvant chemotherapy (40).

In prostate cancer both detection and characterization can be improved by 1H MRS. Normally, citrate containing secrete is produced and released by the prostate gland. This process ceases in malignant cells, which are characterized by low citrate and high total choline levels. From the spectrum the malignant tissues can be distinguished from healthy tissue (41). The information can be used to improve the delineation of the target (42).

Tumour hypoxia is a predictor of treatment failure. 31P MRS can monitor changes in bioenergetics and has been used as surrogate marker of tumour reoxygenation after radiation therapy, mainly in preclinical models (43). MRS of hyperpolarized 13C pyruvate (see below) has been studied as marker of radiation therapy response in a rat model of glioma and was identified as technique that could distinguish pseudo-progression from progression (44).

2.2.5 fMRI

MRI can be sensitive to brain activity. When neural activity increases in a particular area of the brain, the MR signal increases a small amount. The phenomenon is referred to as functional MRI (fMRI, note lower case “f”). There are several underlying mechanisms which together result in the signal change. The neural activity demands oxygenated blood, which has different magnetic properties than deoxygenated blood. However, the main reason for increased signal is that the neural activity triggers a larger change in blood flow in the particular region. Still, the effect is referred to as blood oxygenation level dependent MRI (BOLD).

The signal change in fMRI is small and therefore the acquisition protocol needs to be designed in a special way. In the standard set-up, a subject is performing a task, e.g. finger tapping, according to a paradigm that can be on/off with e.g. 20 s interval during dynamic MRI acquisition. The paradigm may last for many minutes. The acquired data are processed statistically to identify brain areas in which the MR signal has a matching pattern of changes. These brain areas are assumed to be activated by the stimulus of the paradigm. The sensitivity to BOLD changes can be improved by higher magnetic field from a few per cent at 1.5 T to almost 10% at 7 T (45). Integrating fMRI information, i.e. the specific location of different eloquent cortical areas, into the radiotherapy planning process can potentially enable delivery of an adequate radiotherapy to the target while limiting the dose the functional cortex.

In a study of ten patients with astrocytoma, fMRI was performed using four different paradigms, and three treatment plans were issued for each subject: 3D conformal without fMRI information, 3D conformal with fMRI and IMRT with fMRI (46). For both planning techniques including the fMRI information, a significantly higher sparing effect could be achieved in organs at risk. IMRT was also significant better than the conformal plan when the organ at risk was close to the planning target volume. fMRI data was also found useful to spare functional structures in the brain especially in combination with diffusion tensor imaging during radiosurgery of brain lesions (47).

2.2.6 Tissue oxygenation MRI

In many tumours there is an imbalance between oxygen delivery and consumption, leading to hypoxia. The hypoxic environment is known to promote angiogenesis, malignancy, metastases, and genetic instability, to reduce effectiveness of radiation and chemotherapy and additionally hypoxia is associated with poor prognosis of several cancers (48). The oxygenation or degree of hypoxia in the tumour is therefore an important factor, both for designing the therapy, as well as an indicator of the progress. However, non-invasive methods to assess the oxygenation level in vivo are not readily available. There are few methods based on MRI, which potentially could be useful.

One method use 19F MRI perfluorocarbons (PFC). The T1 relaxation time of PFC is very dependent on the local oxygenation. This technique relies on that the PFC needs to be administered into the tumour, either directly or via i.v. injection. It is very hard to get high concentrations PFC into the tumour and 19F MRI accordingly results in very low signal. This technique will not reach outside the area of some preclinical applications.

Another method uses the endogenous contrast mechanism of oxygen on blood. The hemoglobin and deoxyhemoglobin have different magnetic properties and deoxyhemoglobin is strongly paramagnetic. This difference can be assessed by the T2* relaxation time, which will be sensitive to oxygenation. This phenomenon is known as blood-oxygen-level-dependent (BOLD) contrast.

In order to measure the oxygenation with the endogenous contrast mechanism of blood, one often introduces an exposure of 100% oxygen during the measurement. Pure oxygen can be replaced with carbogen (95% O2 and 5% CO2) to avoid the vasoconstriction otherwise induced by oxygen. The change of T2* due to the oxygen exposure will be related to the initial oxygenation. T1 relaxation time is also a parameter of interest in blood. During oxygen exposure, dissolved oxygen (O2) increases five-fold in arterial blood. Dissolved oxygen is

also paramagnetic and the increased oxygenation can be assessed by the T1 relaxation time.

The difference in T2* due to oxygen exposure reflects the deoxyhemoglobin fraction in blood. However, the change in T2* will also be affected by the blood oxygen saturation, blood volume and hematocrit since these parameters influence the blood's concentration of deoxyhemoglobin (48). Therefore, the results may be hard to interpret, unless both T2* and T1 is measured simultaneously (49).

Using carbogen inhalation BOLD MRI has been used to demonstrate improved oxygenation in a range of different tumours. It was possible to identify patients with tumours that responded, on carbogen exposure and who would benefit from carbogen-based radiosensitization (50). Recently, this experimental set-up was verified with immunohistochemisty in a mouse tumour model (51).

The use of T1 in combination with carbogen/oxygen has also been explored on patients with advanced cancer of the abdomen and pelvis. There was significant effect of the oxygen exposure on the tumour T1. Areas with large oxygen enhancement correlated with high perfusion, which also was measured by MRI. Areas with no or little enhancement were attributed to hypoxia, which thereby was possible to identify (52).

2.2.7 Magnetization transfer and chemical exchange saturation transfer imaging

In tissues, it is only the protons in the free water pool, which contribute to the MR signal. Protons in macromolecules (proteins, collagen etc) are tightly bound and have very short T2 and are therefore invisible. However, via magnetization transfer, the bound protons can affect the signal of the free protons. Dedicated RF-pulses are used to saturate the bound proton pool, which will exchange magnetization with the free water. This causes a reduced signal from the free water in tissues in which the magnetization transfer (MT) mechanism is prevalent. Since the extent of signal decay depends on the exchange rate between free and hydration water, MT can be used to provide an alternative contrast method in addition to T1, T2, and proton density differences.

In Chemical Exchange Saturation Transfer (CEST) imaging different signals arising from protons on different molecules are resolved. By selectively saturating a particular proton signal (associated with a particular molecule or an administered agent) that is in exchange with surrounding water molecules, the MRI signal from the surrounding bulk water molecules is also affected. The magnitude of the CEST effect depends on both the exchange rate and the number of ex-

changeable protons. Since CEST imaging contrast reflects exchanging metabolite protons, it is a form of molecular imaging.

In breast cancer, MT has mainly been used to improve the visualization of areas of enhancement in post contrast images. Fibroglandular tissues can be suppressed by 50% (53). Recently, the interest to use MT for tissue characteristic has increased (54). In a study of 60 patients the MT effect between benign and malignant lesions was highly significant and MT was suggested a predictive marker of malignancy (55). Recently, in a study with 41 patients with breast cancer referred to MRI examination, MT was performed in addition to DCE-MRI. There was a significant difference in the MT signal between benign and malign lesions, but DCE-MRI was superior (56).

One application of CEST MRI is amide proton transfer (APT) imaging, which is related to the total protein concentration and thereby the cell density information. The technique has mainly been applied in preclinical models. ATP was able to distinguish between pathology-confirmed regions of tumour and oedema (intracranial rat 9L gliosarcomas), which was not possible with standard T1w/T2w imaging or diffusion weighted (DW) MRI (57). Recently, in a study on patients with different brain tumours ATP was found successful for identification of tumour regions (58). A different application of CEST is discrimination of cancer lesions from fibroglandular tissue in human breast (54).

2.2.8 Hyperpolarized MRI

Normally the signal from tissues in the MRI scanner is created by the polarization of the nuclei, caused by the high magnetic field. However, polarization can also be created by other physical and chemical processes and to levels, which are more than 10 000 times higher than what can be achieved by the magnetic field of clinical MR-scanners (59). This phenomenon has been used to get signal from gases such as 3He or from low concentrations of 13C. Note that the hyperpolarization (HP) is created outside the MR-scanner and outside the body in a dedicated laboratory polarizer. Once the hyperpolarized substance leaves the polarizer and is injected or inhaled in the body, the signal rapidly decays (~1 min). Hyperpolarized 13C is of great interest for application in oncology. In many molecules of interest, a 12-carbon atom can be replaced by a 13C isotope, which subsequently is hyperpolarized. After injection of the hyperpolarized substance can be monitored by MRI, including the metabolism of the molecule. It is worth to note a significant difference between functional studies performed with PET and HP 13C MRI. In PET only the uptake of the injected molecules can be tracked. Using HP 13C MRI the injected molecule as well as its metabolites can be tracked separately, as long

as the process is completed within the time frame given, i.e. ~1 minute.

It is difficult to find a hyperpolarized molecule for which the decay rate in-vivo is slow enough to allow metabolic studies. However, one such molecule is 13C-pyruvate, a key component in glycolysis. From injected 13C-puruvate, dynamic MR studies of the metabolites lactate, alanine and bicarbonate can be performed. Tumours have been proven to have a substantially higher uptake as well as higher metabolic activity of pyruvate (59). HP 13C-pyruvate has been used in many preclinical tumour models. Applications to prostate cancer have gained a special interest. In a mouse model it was possible to use the hyperpolarized lactate as a marker of prostate cancer progression (38). Recently, the first clinical study in man using HP 13C-pyruvate was completed (60). The tumour metabolism in 31 patients with prostate cancer was assessed. The level of 13C-lactate/13C-pyruvate was elevated in regions of biopsy-proven cancer. The technique was also able to detect cancer in regions of the prostate that were previously considered to be tumour–free after examinations with other imaging modalities. Other 13C-agents have been hyperpolarized with success and used in preclinical or in-vitro experimental studies, such as fumarate, glutamine, and acetate (38).

2.2.9 Contrast agents

Contrast agents are used to change the MR signal generated from the tissue. Unlike the contrast agents for SPECT and PET, there is no signal from the contrast agent itself (with the exception of hyperpolarized contrast agents, see above). Neither is there a linear relationship between the contrast agent and a single parameter, such as the attenuation of radiation for contrast media in X-ray and CT applications. The dominating mechanism for changing the signal from tissue in MRI, is to use agents that act on the relaxation properties of the tissue. Paramagnetic complexes of gadolinium have been in clinical use since the late 1980ies as a T1 enhancing agent on T1-weighted images. When cancer cells proliferate and tumours grow a new vasculature is founded and the perfusion increases. However, these neovessels are imperfect, resulting in a leaky vasculature with higher permeability. The gadolinium complexes can easily escape the vasculature and enter the interstitial space, which thereby together with the increased perfusion enhance the tumour.

The T1 enhancement due to gadolinium complexes cannot be classified as molecular imaging since they are nonspecific. Small molecules, peptides, and antibodies can be attached to paramagnetic complexes. The relaxivity of gadolinium complexes in conventional contrast media requires a concentration in the mM range to be detected, which means that the sensitivity of MRI sets a limitation for these

applications. Fortunately, the relaxivity of gadolinium complexes are often increased by attaching macromolecules or nanoparticles to the gadolinium chelates (61). Several approaches have been made and tested in animal models and was recently a subject for a detailed review (61). A peptide sensitive to over-expressed markers of angiogenesis was attached to Gd-DOTA and used to visualize hepatocellular carcinoma in mice. Similarly, tumour specific antibodies conjugated to Gd-DTPA have been tested successfully for MR-imaging of murine mammary carcinomas. Targeted liposomes can be made by incorporating peptides into liposomes that accumulate in tumours.

Another class of contrast agents is built on super paramagnetic iron oxides (SPIO). This class consists of nanoparticles with a core of iron ions covered by layer of for example dextran to prevent aggregating. SPIO are in general particles of size 50 to 3500 nm, while particles smaller than 50 nm is characterized as ultra small (USPIO). These contrast agents alter the magnetic field in their vicinity, inducing signal dephasing with a reduced T2 and T2* as a result. Their effects extend over distances outside their physical location. This property, together with their high relaxivity, makes these agents more potent than conventional gadolinium complexes. It should be noted that the SPIO and USPIO creates a negative contrast on T2- and T2* - weighted images. SPIO and USPIO have a small effect also on T1, but this is normally too small to be useful. So far the greatest clinical value of SPIO and USPIO has been as a contrast media that can distinguish lymph node metastases from normal functioning lymph nodes (62) and for detection of small focal liver lesions (63). Unfortunately, these contrast media has been withdrawn from the market due to safety issues.

Nanoparticles can be designed to accumulate at specific biological targets. The nanoparticles can be attached to molecules such as antibody ligands, peptides, and folic acid (64), and were recently a subject for a detailed review (62). In an animal model of liver cancer, USPIO attached to a protein specific for hepatocellular carcinoma cells was able to identify the malignant cells in MR-images. USPIO linked to a peptide hormone, cholecystokinin, accumulated in pancreatic acinar cells in rats. For breast cancer, nanoparticles were conjugated with a hormone (luteinizing hormone releasing hormone), which accumulated in cells of human breast cancer xenografts, and could act as a contrast media sensitive to metastasis.

It is worth to note that all the above examples of nanoparticles designed for specific biological targets are studies in animals. A limiting factor is the sensitivity. Even in the case of receptors, which are greatly overexpressed in cancerous cells, the ability to link sufficient quantities of the contrast agent to the target to produce a detectable contrast

change in the MR image is limited (62). Thereby, the possible application to humans will be hampered. Additionally, there are the restrictions from the regulatory authorities. At present no SPIO or USPIO approved by FDA for human use is commercially available.

2.2.10 MR-elastography

MR-elastography (MRE) is a method for measuring the mechanical properties of tissue. The mechanical properties can change dramatically due to pathologically processes, such as cancer, fibrosis or inflammation. This is of course a well-known effect, which also is the basis for manual palpation, which has been a diagnostic tool for centuries. However, palpation has limitations with respect to the depth of the tissue, volume and subjectivity. MR-elastography can assess the tissue properties in large volumes and the measurement also results in quantitative information on stiffness.

Mechanical waves, referred to as shear waves, are generated by an external acoustic driver, actuator, for low frequency vibrations. The shear wave displacements in the tissue can be monitored by motion encoded phase contrast MRI. The temporal and spatial characteristics of the wave field form the basis for an algorithm that transforms the obtained data to a map of the tissue mechanical properties.

The main driver for the clinical development of MRE is applications to liver diseases. MRE is evolving as a non-invasive alternative to biopsy in detection and staging of chronic liver fibrosis (65). In contrast to biopsy MRE is non-invasive. Additional biopsies only reflect a few samples and are subject to sampling errors, while MRE examines the whole organ. In patients with suspected hepatocellular carcinoma MRE has also been found able to distinguish between malignant tumours from benign lesions (66). MRE has been used in diagnostic studies of the breast as a complementary method to contrast enhanced MRI. In a study of 57 suspected breast lesions both CE-MRI and MRE was performed. The diagnostic accuracy was significantly increased when the MRE was added to the protocol. However, the lesions were rather large and easily palpable (67). The prostate is a challenging organ for MRE in cancer applications. The organ is centric located in the body and waves from an external actuator attenuate in the surrounding tissue. An alternative approach is an intra-cavitary endorectal actuator (68). The proposed technique seems very promising with good acceptance and repeatability. At present this technique has only been tried out on volunteers and a limited number of patients. In summary MRE is technique with great potential, but there is need for technical improvement and especially validation of the technique against other measures.

2.3 Summary

As indicated above many functional MR-methods are available. Although many of the methods have been available for diagnostic radiology for decades, not many methods have been established as a standard tool in clinical routine or even in clinical research trials. There are several explanations: Often the functional methods are complicated and technically challenging both for operators and equipment. The methods may require special analysing software not supplied or available by the vendors of MR-scanners. There are no established standards for data acquisition and data analysing. Additionally, the quantitative data that is the result of the FMRI do not always add substantially to the diagnostic procedure in the clinical routine. However, it is worth to underline that one of the strengths of the functional methods is that they do result in quantitative data. The working potential of quantitative MR-methods is enormous, if the effort to bring these functional methods into robust and validated biomarkers is taken by the imaging community. At present the functional methods, which are the most elaborated at present, are CE-perfusion.

There are several on-going initiatives to standardize FMRI. The Radiological Society of North America started the Quantitative Imaging Biomarkers Alliance (QIBA). Within that framework task groups are working on standardization of for example MR-perfusion, diffusion, flow and fMRI. At present the only reports available from QIBA are from nuclear medicine task groups. There are other initiatives on this subject from the American Association of Physicists in Medicine and National Cancer Institute. Similarly the reports are still pending.

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3. MRI in treatment selection and target definition

3.1 Present status

MRI is used today for anatomical delineation of tumours in order to increase accuracy of target volume delineation. Most radiotherapy department in Sweden use diagnostic MRI as a basis for target delineation to some extent i.e. for brain tumours, pelvic malignancies and head and neck cancer. Fusion of MRI and CT images are performed but the usefulness is hampered because the MRI has not been performed in treatment position. Many MRI scanners used today in Sweden cannot perform an examination with an immobilized patient due to too narrow gantry opening.

3.2 Definition of target volumes

Target volumes, GTV (Gross Tumour volume), CTV (Clinical Target Volume) and sometimes ITV (Internal Target Volume) may be delineated on MR-images with MRI made in treatment position, and after good image registration with the planning CT images. Different MR-series can be registered together with CT for different use in the delineation procedure; e.g T1w-sequences can be used for optimal registration of bone structures, T2w-sequences is usually the best imaging method for the tumour and soft tissue in the pelvic area. Diffusion weighted imaging and other techniques can be used for help in defined areas (1). The delineation should be done according to ICRU definitions (ICRU report 83)(2). GTV is delineated without margin and should have a clear and unambiguous index e.g. GTV-MR rectum (imaging modality and anatomical region). In delineation of the CTV-MR, the improved discrimination of soft tissue and vessels is of advantage and contrast agents may sometimes be omitted. PTV-MR is generated according to each RT department's own statistics of uncertainties including registration uncertainties. MR-techniques are described for estimations of uncertainties and margins (3). In prostate cancer, implanted position markers are frequently used, as yet without documented clinical problems in the magnetic fields.

3.3 Future possibilities

MRI has been used to improve staging and predict response of treatment in a number of diagnoses. In the future, FMRI might be used to detect areas suitable for boost or detect areas of e.g. hypoxia (4). Below the current and future use of MRI in treatment selection and target

definition are exemplified. Previous studies are mainly performed in prostate, rectal cancer and cervical cancer (5-8).

3.3.1 Prostate cancer

Localised prostate cancer is today treated with surgery or radiotherapy. The treatment decision is based on local tradition and patient's choice. At present, MRI is used primarily for the staging of disease in biopsy-proven cancer and to select patients with localized prostate cancer to radiotherapy by a more accurate detection of metastatic spread (9). MRI also has a role in target definition of radiation therapy, both conformal or intensity-modulated external beam radiation therapy, and guiding of interstitial seed implant or brachytherapy. MR-based brachytherapy in prostate cancer is under development (10). The evidence for MRI in staging of prostate cancer is questioned (11,12).

In the future, prostate MRI might also be used to accurately characterize focal lesions within the gland, an ability that can lead to guidance for biopsies to the most malignant parts (13) and definition of areas suitable for boost. In RT of prostate cancer it is aimed for and technically possible with IGRT to deposit high RT doses to biologically high-risk areas. These areas, GTV, can be visualized and delineated with MRI in treatment position (14), sometimes with special techniques e.g small field of view excitations using parallel transmit technology - or, functional MRI (FMRI), as diffusion or perfusion (15).

MRI could also be used for selection of patients suitable for pelvic lymph node irradiation (16) although a recent study did not find any advantage of diffusion weighted MRI over CT or choline PET (17). Furthermore, MRI has been shown to be suitable for detection of seminal vesicle invasion (18).

3.3.2 Cancer of the uterine cervix

Patients with localised cervical cancer are today managed by a multimodality approach including surgery, chemotherapy and radiotherapy, both external and brachytherapy. MRI is the preferred modality for staging of cervical cancer at many departments and is also used to direct the brachytherapy and thereby possibly improve outcome. For brachytherapy in cervical cancer, individually, MR-based RT-planning is well documented. Target volumes are e.g. according to GEC-ESTRO guidelines, recommended to be delineated on the MR images (19).

In a retrospective study of image guided brachytherapy based on MRI, reduced morbidity and improved survival of cervix cancer was seen (20). In the future, MRI can serve as a basis for adaptive radiotherapy

due to changes in tumour extension during the RT treatment time. Furthermore, MR based methods for treatment selection of patients suitable for proton boost (21) and contrast compounds aimed to detect hypoxic areas suitable for boost (22) , are under development.

3.3.3 Rectal cancer

Current principles of treatment of localised rectal cancer include radiotherapy, sometimes in combination with chemotherapy and surgery. Radiotherapy is most often given preoperatively but can be the only treatment in old and frail patients. MRI plays a pivotal role for staging and management of rectal cancer and is used in the diagnostic work up. The extent of the disease as lineated on MRI governs the choice of therapy e.g. preoperative chemoradiotherapy to locally advanced disease. In the future, FMRI might be used to detect biological features in rectal cancer e.g. ADC has been shown to predict tumour grade (23). High resolution MRI has been shown to be predictive of intramural invasion in rectal cancer (24). Furthermore, extramural depth as measured with ADC was correlated to poor outcome in T3 rectal cancers (25). MRI might be used to define the target for an integrated boost in adaptive radiotherapy of rectal cancer (26).

Even if MRI in staging of pelvic tumours is not documented superior to CT, MRI in treatment position may be of great value in target delineation in specific situations when the CT imaging is suboptimal such as:

1. Delineation of the prostate gland, specially the caudal border
2. Delineation of local tumour extension in cervical cancer
3. Delineation of low rectal cancer
4. Delineation of anal cancer

3.3.4 Brain tumours

Brain tumours constitute a heterogeneous group where radiotherapy is commonly a part of the treatment. MRI is a cornerstone in the diagnosis of brain tumours. The modality of choice today for target definition is CT but MRI could be used in gliomas to reduce the irradiated volume (27). MRSI (Magnetic Resonance Spectroscopy Imaging also known as CSI) have been used to differentiate radiation dose in gliomas by dose painting (28). MRI is also promising in detecting the effect of new anti-angiogeneic agents on glioma after radiochemotherapy (29).

Though MRI of the brain is the imaging modality of choice for RT of brain tumours, pre- and postoperative MRI have been registered with

CT for RT planning and used for some years (30,31). Then MRI was not often performed in treatment position with the registration being suboptimal due to the time factor, different position of the skull etc. Many studies of target delineation with the use of FMRI have been reported (32).

3.3.5 Head and neck cancer

Patients with squamous cell carcinomas (SCCs) of the head and neck are commonly treated with radiotherapy. Imaging plays a critical role in helping define the targets for radiation therapy, especially in highly conformal RT e.g. IMRT. Anatomic imaging with conventional modalities, particularly CT is used in patients with head and neck SCCs, but this approach has limitations. MRI circumvents some frequent problems connected with CT such as, major artefacts from dental fillings and implants. It also gives an improved soft tissue contrast and may thus give additional anatomical information. A common problem in connection to RT is that patients need to be investigated in their treatment position in immobilisation devices, which hampers the use of optimal MR-coil configurations. This, together with internal movements (e.g. swallowing during image acquisition) still seems hold back a more extensive use of MRI in the head and neck region. In the future, MRI might provide important information for target definition (33). It is also concluded MRI offers a better opportunity to define the border between normal tissues and tumour (34).

In radiotherapy of head and neck cancer, PET has been the most studied technique to define biologically active high-risk areas (35). The use of FMRI in the radiotherapy planning aspect has not been extensively studied.

In the head and neck region, some studies are made of MRI in the RT planning setting (34,36). Development is ongoing with optimizing MRI protocols and coils to fit the patients in treatment position (33). Scanning time has to be reduced compared with the diagnostic situation. Better moulding/positioning techniques are also under development. In this region a more individualized MR-setting is needed than in the pelvic region, e.g. also need for intravenous contrast in some MR- acquisitions.

The conclusion for head and neck cancer is that MRI has an important role in delineating the target volume in many cases. The sensitivity of MRI for detecting tumours in the head and neck is similar to that of CT. The role of MRI in monitoring treatment effect is not yet established.

3.3.6 Lung cancer

For lung cancer, radiotherapy is used for all stages of the disease. In localized lung cancer stereotactic body radiotherapy is an alternative to surgery, in locally advanced lung cancer radiotherapy in combination with chemotherapy offers a possibility for curative treatment and for advanced disease palliative radiotherapy offers effective symptom relief and local tumour control. Radiotherapy for lung cancer is associated with a few well-known culprits. Due to breathing many lung tumours are subject to significant intrafraction movement making solutions such as 4D CT planning, gating or even tracking necessary. Selection of patients for radiotherapy is mainly based on staging using CT and PET/CT. CT offers excellent anatomical information while the metabolic information from FDG-PET improves the possibility to find pathologic mediastinal lymph nodes. MRI is not used for lung cancer staging today and is only used for the precise mapping of apical (pancoast) tumours where the superior soft tissue characteristics of MRI is an advantage.

In the future, MRI offers several characteristics that are being evaluated for treatment selection. Dynamic contrast enhanced MRI and diffusion weighted MRI have gained attention for early assessment of tumour response (37-39). 3He hyperpolarized MRI have recently been utilized for assessment of risk for normal tissue damage (40) and treatment outcome. Diffusion weighted MRI is proposed to have predictive information of early response during chemoradiotherapy for locally advanced lung cancer (37). MRI has also been proposed to be of value for auto-contouring of target volumes (41), tracking tumour movements (42) and for 4D studies of target movement (43).

3.3.7 Breast cancer

In RT planning for breast cancer, it is reported that MR is a good imaging technique for visualizing breast tissue (44), still uncertain if MR is superior to CT and of clinical importance in the routine management. However, for delineation of boost volumes a better technique than x-ray based CT scans is needed.

3.4 Organ at risk definition

MRI is superior to other imaging modalities also for definition of organs at risk (OAR). After MR registration with the planning CT, it is important to use the same imaging modalities for delineation of target volumes and OARs to avoid introducing new uncertainties. ICRU definitions should be used also for delineation of OARs. This may be relevant for many tumour sites including the brain where fMRI have been used for sparing critical volumes (see chapter 2.2.5).

3.5 Summary

MRI is a modality assumed to improve delineation of RT target volumes and organs at risk, e.g. in specific areas of the tumour or normal tissue in the pelvis, brain and head and neck region. MRI might also be useful for characterization of focal lesions and definition of volumes suitable for boost and adaptation of RT due to time dependent changes in the target volume.

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4. Treatment planning and practical issues

4.1 Present status

As described in previous chapters, MRI may often provide valuable information for the definition of radiotherapy treatment planning volumes. At present, this information is generally utilised through a hybrid approach, where target volumes delineated on MR images are transferred to a reference CT, acquired specifically for treatment planning purposes. The treatment planning CT is used to define an accurate, undistorted geometrical frame of reference, and to provide the basic radiation interaction data that are required for 3D dose calculations. Thereby, the hybrid approach ensures that the absorbed dose calculations can be carried out according to conventional standards. In addition, the CT is normally also used to create reference images for subsequent image guided radiotherapy (IGRT) procedures at the treatment machine.

In order to transfer the MRI information to the treatment planning CT, the two image data sets have to be co-registered. By using rigid co-registration methods average displacement errors in the order of 2 mm have been reported for cranial (1), pelvis and prostate (2), and prone rectal cancer patients (3). If the patient is adequately immobilised, this level of accuracy can be obtained with rigid transforms also in the more flexible head-and-neck region, or else deformable registration methods may be required (4). In regions with significant organ motion larger uncertainties may be expected, and for anatomical landmarks in the abdominal region average displacement errors over 5 mm have been reported (5). It should be noted, that these are average values, and that larger deviations do occur.

Good radiotherapy practice requires a geometrical accuracy in the order of millimetres (6). In order to avoid the uncertainties associated with image co-registration and the transfer of structures from MRI to CT, it has therefore been proposed that MRI could be used as the only input to the treatment planning process (7-9). An MRI-only approach simplifies the work-flow, which has advantages both for the department, in terms of reduced workload and cost, and for the patient with reduced number of examinations. However, there are also challenges associated with the integration of MRI in each step of the treatment planning process from patient set-up to absorbed dose calculations, and some of these issues will be discussed in this chapter.

4.2 Patient set-up and immobilisation

For radiotherapy treatment planning, it is important that the patient can be positioned in treatment position during imaging. Conventional MR scanners in diagnostic radiology generally have small and deep openings and non-flat table tops, which makes it difficult to position the patient in treatment position with the immobilisation device to be used at treatment. This means that a dedicated MRI scanner is preferred for radiotherapy. Furthermore, external alignment lasers for isocenter and skin markings are often lacking in a diagnostic MRI installation. Today, there are open and wide-bore scanners on the market (70 cm), which can be equipped with a flat table top and external alignment lasers, and with plenty of room to accommodate the patient in treatment position, similar to a CT scanner with good ergonomics (10,11).

The main difficulty with radiotherapy immobilisation devices in MRI is the limited space available when using head imaging coils. An alternative possibility is to use the more flexible surface coils, but it has been feared that these may lead to a reduced contrast-to-noise ratio and thereby lessen the usefulness of MRI for target delineation. It has been shown, however, that by applying adequate uniformity corrections, satisfactory image quality can be obtained by using a cardiac coil arrangement (12).

Most materials used for thermoplastic masks and other immobilisation devices are MR compatible, but it is important to make sure that even small parts, such as nuts or bolts, are also compatible. In particular, carbon fibre, which is used frequently in radiotherapy due to its light weight and low attenuation, may not be MR compatible. This could be replaced, for instance, by composite materials with similar properties (13).

4.3 Image distortion

Image distortion in MRI can be either system related or patient induced. System-related distortion is often quantified by using a phantom with evenly distributed grid marker points, for instance, a plastic container with regularly spaced holes filled with a contrast producing agent. The distortion is then measured as the deviation between the observed and true grid positions (10). For 1.5 T and 3 T wide-bore scanners it has been demonstrated that system-related distortion can be within 1 mm, at least in the central parts of the images (10,11,14).

Patient-induced distortion is due to effects such as susceptibility changes and chemical shift differences. In clinical brain MRI for radi-

ation treatment planning these effects are generally less than 1 mm (15), which is compatible with conventional radiotherapy practice (6). The effects increase in the presence of air cavities, however, and may become considerable in the head-and-neck and thorax regions. Recent work has addressed methods to investigate and reduce these effects (16). Finally, it should be noted that for certain pulse-sequences optimised for functional imaging, e.g. diffusion weighted MRI, the effects of patient-induced distortion can be substantial (17).

4.4 Absorbed dose calculations

In an MRI-only approach to treatment planning, the basic radiation interaction data required for 3D dose calculations has to be derived from the MR images. This is not entirely straightforward, since MR does not reflect the way conventional radiotherapy beams interact with matter. It is possible, however, to create a "synthetic CT" by using the anatomical or structural information from MRI, and by assigning a reconstructed value to each voxel based on assumptions or calculations. The two main groups of methods for creating MRI-based synthetic CT for treatment planning dose calculations will be discussed in the following.

4.4.1 Anatomy-based conversion

One practical approach to MRI-based dose calculations is to assign common interaction properties to partial volumes defined in the patient. In its most simplistic version this could mean defining the whole patient as composed of water, while more elaborate alternatives would use a set of several segmented volumes, such as soft tissue, bone, lung and air cavities. This can be done with a dosimetric accuracy better than 2%, although a manual segmentation of the involved volumes is too time-consuming for clinical use (18-20). It should be noted that these figures relate to the prescription dose, and that larger uncertainties may occur in low-dose regions.

Another type of anatomy-based conversion relies on the construction of coupled MR and CT atlases (21). For an individual patient, the MR atlas is co-registered with the patient's MR images. The resulting transform is then applied to the associated CT atlas, thus providing a synthetic CT for the individual patient. The synthetic CT derived in this way has been used for dose calculations in prostate patients, deviating from full CT-based calculation with less than 2% (21). It should be beared in mind, however, that this method propagates the uncertainties introduced in the image co-registration procedure, and that its accuracy therefore can be sensitive to anatomical anomalies.

4.4.2 Voxel-based conversion

A more general way to produce a synthetic CT is to use an algorithm capable of calculating proper voxel values based on the information contained in the MR images. It has been shown that it is possible to create robust, synthetic CT in certain regions of the body by combining the information from a T2-weighted spin-echo MRI with two different ultra-short echo-time (UTE) sequences (22). This method adds only a few minutes for the extra MR-examinations, is insensitive to anatomical variations thanks to its general voxel-based approach, and is easy to integrate with the conventional treatment planning workflow. For intracranial treatment planning studies this method has been found to yield an accuracy comparable to anatomy-based conversion methods (23). While it has been demonstrated that the UTE sequence provides improved differentiation between bone tissue and air cavities in the head-and-neck region (24), other authors have investigated the possibility to derive synthetic CT from only one T1/T2*-weighted gradient-echo MRI with promising results (25). Ongoing work aims at generalising the applicability of voxel-based conversion methods to other anatomical areas.

4.5 Reference images for IGRT

As MRI was introduced in radiotherapy primarily due to its superior soft tissue contrast and its advantages for target delineation, it was anticipated already from the beginning that MRI, thanks to its 3D-multiplanar capability, could also be advantageous for IGRT. For conventional treatment units equipped with x-ray portal imaging it has been shown that the accuracy of set-up verifications based on reconstructed MRI images can be equivalent to that using CT-based digitally reconstructed radiographs (DRR) (21,26).

In order to fully utilise the anticipated advantages with MRI-based IGRT, treatment machines with integrated MRI would be required. Such machines are indeed under development (27,28). Within the foreseeable future, however, most clinics who want to introduce MRI for radiotherapy preparations will have the MRI unit located in another room, separated from the treatment room, at best with a trolley system for patient transport between the units (9). MRI-based procedures for IGRT and treatment response assessment are further discussed in chapter 5.

4.6 Summary

An MRI-only approach to treatment planning has been proposed in order to avoid the uncertainties associated with image co-registration. This means that dose-calculations need to be performed by using synthetic CT, derived from MR information. In order to avoid co-

registration uncertainties altogether, voxel-based synthetic CT is an attractive approach. The associated dosimetric uncertainty should be acceptable, and ongoing work aims to further improve the accuracy and applicability of these methods. In conclusion, although there are certain remaining issues with regard to MRI-based treatment planning and absorbed dose calculations, practical solutions are well within reach.

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5. Treatment and follow up

5.1 Present status

Today, the common standard for verifications during the course of treatment is based on CT imaging, cone beam CT (CBCT) or orthogonal planar MV- or kV-images (radiographs). A DRR is usually constructed from the planning CT and used as a reference for verifications at treatment. MRI has potential to make improvements in this area because of the improved information due to superior soft-tissue contrast and functional imaging possibilities as well as the possibility to do patient examinations at each treatment fraction without additional radiation dose to the patient. Using MRI for verifications during the course of treatment at a large scale requires a dedicated MRI scanner in the radiotherapy clinic. Today, this is becoming a reality at more and more clinics in Sweden and over the world. The use of MRI for verifications during the course of treatment in clinical practice can therefore be expected to increase in the near future.

Common practice for assessment of tumour response to radiotherapy is today based on monitoring tumour size and volume on CT- or MR-images. MRI is used in follow-up for children and for testicular cancer to avoid radiation exposure from CT. Several studies have demonstrated the great possibilities with functional and metabolic imaging techniques of MRI to be used as early predictors of tumour response to therapy (1). The technique needs further validation in clinical studies before being introduced in clinical practice.

5.2 Treatment verification and adaptation (image guided radiotherapy)

To achieve the benefits of conformal treatment techniques, high precision on target delineation and determination of target margins are required. The determination of target margins is based on inter- and intra fraction variations of the patient geometry. While it is essential to estimate inter- and intra fraction variations of the patient geometry prior to treatment to make correct determinations of target margins it is just as essential to verify the inter- and intra fraction variations during the course of treatment for verification and adaptation of the treatment. The efficiency of radiotherapy is depending on precision of target irradiation. To be able to do MRI for set-up verification the image guidance system needs to be calibrated with direct links to the coordinate frame of the treatment machine and the total time between imaging and the end of treatment needs to be limited to prevent large

patient movements between imaging and treatment. A solution with a dedicated trolley to transport the immobilized patient fixed to the table top between the treatment machine and the MRI scanner located in an adjacent room has been described (2). Other suggestions are based on an integrated MRI/radiotherapy device (3,4).

5.2.1 Inter fraction verification

A dedicated MRI scanner at the radiotherapy clinic with possibilities for doing imaging of the patient in the treatment position has the potential to do precise set-up treatment verification for soft tissue tumours without the need for invasive fiducial markers. Although MRI was introduced in radiotherapy primarily due to its superior soft tissue contrast and its advantages for target delineation, it was anticipated that MRI thanks to its 3D-multiplanar capability could also be advantageous for beams eye view (BEV) image reconstructions and for treatment simulation (5). It has later been shown that set-up verifications based on reconstructed MRI images can be equivalent to using CT-based DRRs (6).

In external beam radiotherapy, changes in patient anatomy during the course of treatment, for example tumour shrinkage, variations in bladder and rectal filling or weight loss, influence on the optimal choice of treatment volume. In patients with cervical cancer, weekly MRI scans during radiation treatment was studied to derive general target margins for this patient group (7). Taking this one step further, regular MRI scans during the course of treatment would give possibilities to adapt the treatment volume for the individual patient following the changes in patient anatomy. Adaptive treatment protocols can be constructed either based on a choice of the day from a library of treatment plans or on online re-planning. This type of adapted treatment implies a minimization of the dose to limiting normal tissues in the vicinity of the target volume and thereby an improvement of the therapeutic ratio. The advantages with adaptive treatment strategies for cervical cancer patients that takes bladder filling into account has been documented (8). Furthermore, changes in patient anatomy are a major concern for proton and ion therapy where changes in the geometry even far from the target volume can give significant changes in the delivered dose distribution due to the physical nature of the particle beam. Accurate registration of and adaption to the changes in patient anatomy during the course of treatment is therefore important for ion treatments. MRI-based treatment plan adaptation for ion therapy has been studied (9). The limited visibility of the tumour itself using CT-based imaging techniques and the excellent visualization of both tumour and surrounding organs at risk using MRI makes the MRI technique for registration of changes in patient anatomy during treatment superior.

MRI guided radiotherapy has been more commonly implemented for brachytherapy as compared to external beam radiotherapy. The Medical University of Vienna radiotherapy department has been doing patient specific MRI-based brachytherapy treatments for cervical cancer since 2002 and their method of personalised dose adaptation is documented (10). MRI-guided brachytherapy for cervical cancer has been shown to give possibilities to optimize tumour coverage and decrease dose to critical normal tissues (11).

5.2.2 Intra fraction verification

Continuous tumour and organ motions can be studied using dynamic MRI analysis. The extent of intra fraction motions has for example been analysed in pretreatment studies of prostate (12), head and neck (13) and oesophageal tumours (14). Such studies are valuable for determination of planning target margins. An integrated MRI/radiotherapy device (3,4) makes it possible to produce MR images at the same time as irradiation and can therefore also be used for on-line, intra-fraction image guidance. The advantages of such image guidance was demonstrated in a study of intrafraction CTV motions in patients with cervical cancer (15). An integrated MRI/radiotherapy device could, furthermore, be used for on-line treatment adaptation such as MRI based tracking (16,17) and gating (18) to compensate for tumour motions in real time. The effect of MRI based gating was studied theoretically for treatments of renal cell carcinoma (19). The use of an integrated MR/radiotherapy device is still far from common clinical practice and further studies will give information on the usefulness of such a device. For fully taking advantage of such equipment it seems logical that the treatment planning is shifted towards an "MR-only" work-flow.

5.3 Radiobiology based adaptive radiotherapy

Functional and metabolic imaging techniques of MRI such as DW-MRI, dynamic contrast-enhanced MRI (DCE-MRI) and magnetic resonance spectroscopy (MRS) with ability to detect physiological and morphological changes in the tumour have possibilities to be used as early predictors of response to radiotherapy (see chapter 2). The use of functional and metabolic MRI for response assessment has been investigated in several preclinical studies but recently also in a few clinical studies (1). Functional changes in the tumour occur well before macroscopic indicators of response such as change in size, which is common standard for estimation of response today. Early prediction of tumour response would identify an ineffective treatment at an early stage and give a good foundation for personalised, adaptive radiotherapy. In this sense, adaptive radiotherapy means modifying and cus-

tomizing the treatment regimen according to the predicted response to the treatment for the individual patient.

Most clinical studies on the use of functional MRI during radiotherapy as a biomarker of radiotherapy treatment response have been done on brain tumours (1) but there are also a number of studies on other diagnoses such as rectal-, prostate- cervical- and liver cancers and recently a few on tumours in the head and neck region. The majority of those studies are based on using DW-MRI to predict early response. The potential to predict radiotherapy treatment response for glioblastoma patients during radiotherapy has been demonstrated (20). An early evaluation of the effectiveness of radiotherapy is of special concern for this patient group since the glioblastoma response is fast and the time of survival for those patients is short. However, validation of consistency between different equipment and of measurements over time and further validation on the correlation between imaging parameters and response is a prerequisite before use in clinical routine (21). Assessment of tumour response to combined chemoradiotherapy of rectal cancer using DW-MRI has been studied in small patient groups (22-24). An early assessment of response would in this case be beneficial to identify the patients with low response to the initial chemotherapy to be able to individually adapt and intensify the radiotherapy treatment. Improvement of prostate cancer radiotherapy is still an issue (25) and an adaptive radiotherapy treatment protocol might be one of the possible solutions to achieve this. The radiotherapy response of prostate tumours (measured as PSA response during one year) was best detected by ADC at 6 weeks of therapy in a study of 19 patients (26). The authors emphasize the need for further investigations. Initial positive results of using functional MRI during radiotherapy to predict early response to treatment have also been reported for other diagnosis worth mentioning, for example for cervical cancers (27), liver cancers (28) and tumours in the head and neck region (29). Most studies on this issue are made based on a limited number of patients. The initial results are promising but further studies will be needed before performing radiobiology based adaptive therapy based on functional MRI.

5.4 Radiotherapy follow-up

MRI is already frequently used for radiotherapy follow-up. However, the use of functional MRI for follow-up is not common practice but has shown promising possibilities to be used for prediction of tumour response as discussed in section 5.3. A few studies have also shown possibilities for using functional MRI for follow-up on normal tissue complications, for example the use of DW-MRI for evaluation of salivary gland function after radiotherapy (30).

In brain tumours, differentiation between recurrence and radionecrosis is a critical step in the follow-up management of patients treated with radiotherapy. A method that can reliably differentiate tumour recurrence from radiation necrosis using standard MRI sequences would be of significant value (31). Both pseudo-progression and pseudo-response have been described where pseudo-progression corresponds to radionecrosis and pseudo-regression to regress of the oedema component, most often after anti-angiogenetic therapy (32). MRI has also been used to evaluate late radiation effects in the brain.

5.5 Summary

Implementation of an MRI scanner at the radiotherapy clinic with direct links to the coordinate frame of the treatment machine and with possibilities for doing imaging of the patient in the treatment position would introduce new possibilities for set-up treatment verification and adaptation of the treatment volume according to the changes in patient anatomy. An integrated MRI/radiotherapy device would furthermore make it possible to do on-line intra-fraction image guidance and treatment adaptation such as MRI based tracking and gating. However, the use of such a device is still far from common clinical practice. Functional and metabolic imaging techniques of MRI have shown great potentials to be used for early predictors of tumour response to radiotherapy as well as for follow-up. An early prediction of tumour response would make it possible to adapt the treatment according to the response. Although the initial results are promising, further validation studies will be needed before performing radiobiology based adaptive therapy based on FMRI.

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6. Practical aspects of the introduction of MR in radiotherapy

6.1 Organisation

MRI was introduced for clinical use more than thirty years ago. The basic physics behind MR and its technical potential contributed to the need for multidisciplinary management when it was introduced in the radiological departments. MRI has gradually become more, but not fully integrated among other imaging modalities in radiology departments. The complex physics, the versatility as well as important safety issues are possible reasons why MR-centres are common with dedicated staff only working with this modality.

When MRI is introduced in radiotherapy and in particular when MRI is being installed in radiotherapy departments, new categories of staff are involved together and assigned new responsibilities. In this situation, departments form new extended multidisciplinary teams. These teams are especially important when planning and initiating MRI in radiotherapy (NHS IGRT report 2012: www.sor.org).

An education plan should be part of planning for establishing MRI in radiotherapy. The multidisciplinary team is a reasonable core to start an education program focussed on patient and staff safety issues, basic MR physics and clinical applications including specific applications for radiotherapy and patient set up procedures.

6.2 Safety

A complete MRI installation is equipped not only with a dedicated shielded examination room but also exterior facilities that prevent people from entering by accident, bringing magnetic implants or equipment into the scanner room. All facilities with the purpose of being used in the MR room has to be non magnetic and compatible as such. When installing MRI in a radiotherapy department this is important since both the aspect of facilitated workflow and safety has to be considered.

6.2.1 Metallic implants

Routines for identification of patients with implants that are not compatible with MRI are established in all radiology departments. When initiating MRI in radiotherapy departments it is logical to copy these routines as far as they can be transferred. Even metallic implants com-

patible with MRI such as hip prostheses may be a challenge when within the field of view since they cause artefacts that cause image distortions and degrade general image quality. Conventional fiducials intended as markers for target in radiotherapy are not necessarily well visualised on MRI and there is ongoing development using dedicated fiducials for this purpose.

6.2.2 Contrast agents

When using MRI for radiation treatment planning, T1- and T2-weighted sequences of the planning volume are performed but contrast agents are not routinely administered. Contrast agents are neither routinely administered when radiation dose planning is performed using CT. For this reason, routines need to be established in the radiation department both for screening of patients for impaired renal function, previous severe reactions to contrast agents as well as time and dose for previous contrast administration. Guidelines for such screening are available at the Swedish Society for Radiology (www.sfbfm.se).

6.2.3 Claustrophobia

Claustrophobia is a potential contraindication for MRI but has to be taken into its context and when necessary discussed individually with the patient. Correct patient management contribute to the patients experience of MRI. If claustrophobia exists together with strong clinical indication to perform MRI the possibility to perform MRI under general anaesthesia may be considered. Offering the patient a visit to the MR unit to see and lie down in the camera a separate day before the actual examination is useful to ascertain whether the patient tolerate the examination or not.

6.2.4 Diagnostic findings on MRI

When MRI is performed for radiotherapy treatment planning it is important to have a previous, usually not older than 4 weeks, diagnostic examination at hand together with the radiologist report. This is important because MRI when performed for radiotherapy planning is not performed for comprehensive TNM-staging of the tumour. Even so, the MR examination, even when performed with only T1-and T2-weighed images contain morphological information, both concerning the primary tumour as well as concerning locoregional and distant metastases if included in the field of view. The extent of additional diagnostic information in MR images not picked up in a radiation department is not known, neither cancer relevant information or incidental findings.

6.3 Technical challenges

There are several technical challenges when MRI is integrated in the radiation therapy workflow. There are practical aspects, e.g. the table top in the MR-camera needs to be identical to the one used during therapy, the fixation devices for radiation therapy set-up needs to be adjusted to fit within the opening of the magnet and the coils of the scanner needs to be compatible to fixation devices and optimized for a radiation therapy geometry (1). All of these issues are at present addressed by the main MR-camera vendors but there is still room for considerable improvement.
The geometric accuracy of the MR-scanner is not as good as for CT. The geometric distortions of the MR-scanner are dependent of the main magnetic field and the gradient system. Modern systems have dedicated and sophisticated correction algorithms for these effects. Additionally, large susceptibility differences within the body such as air cavities and metallic implants may cause geometrical deviations (2). It is important that the use of MRI for radiation therapy is associated with reliable quality assurance program to monitor the geometrical distortions.

Another susceptibility issue may be introduced by the fiducial markers used for example in prostate to monitor the position during radiation therapy. The markers should be visible both on MR-images as well as X-ray kilovolt or megavolt imaging. Some susceptibility effect of the marker may be needed to identify them clearly on MR-images (3). However, the same susceptibility effects of the marker may hamper the possibility to use functional imaging techniques such as MR-diffusion of the organ of interest (4).
If the intention is to replace the CT with MRI, there is one limitation of MRI important to consider. Information similar to the attenuation data given by CT, which often is needed by the treatment planning systems, is not available from MRI. However, there are several promising techniques that address this issue (5).

MR images obtained in the radiotherapy department should also be routinely reviewed to guarantee optimal imaging quality and to screen for technical errors (NHS IGRT report 2012: www.sor.org). At present, cross sectional images obtained for radiotherapy planning purposes are not routinely reviewed by diagnostic radiologists.

6.4 Research

Introducing MRI in radiotherapy, in particular when MRI is installed in the radiotherapy department, facilitate research in all areas related to radiotherapy. As compared to an installation in a radiological department, the patient may have scheduled appointments at the radiation department several times before and during treatment. This opens

for the possibility to use these appointments also to include the patient in research projects with multiple serial MR examinations that would not be feasible in a radiology department. Furthermore, the team working with the treatment of the patient is the natural source for identifying areas in need for research.

An area with a high interest in research focus, with several examples in this report, is functional MR imaging. Some of these imaging techniques, such as DCE-MRI and 1H MRSI has been used in clinical trials for more than two decades. Despite this, the introduction of these techniques has been limited in a wider context, mainly due to the technical prerequisites and level of standardisation they offer. When RECIST was revised to RECIST 1.1 it was concluded that there was insufficient data to include functional imaging techniques such as PET or DCE MRI in the response evaluation criteria (6). There are presently several ongoing activities aiming at facilitating standardisation of functional imaging techniques. One of these activities was initiated in 2010 by the National Institute of Health for volumetric CT, PET CT and DCE MRI (https://wiki.nci.nih.gov/display/CIP/QIBA+DCE-MRI). There are also ongoing activities at EORTC aiming at standardising functional imaging techniques for clinical trials (http://www.eortc.org/research-groups/imaging-group/achievements).

6.5 Summary

The introduction of MRI in radiotherapy comes together with challenges regarding forming multidisciplinary teams, education and quality assurance. The multidisciplinary team has an important role to deal with safety issues and routines related to MRI.

6.6 References

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7. Organisation and implementation of MR in Swedish radiotherapy

7.1 Organisation

Cancer radiotherapy in Sweden is entirely a part of the general health care system. Six regional cancer centres have the responsibility to organize cancer care within each region and to coordinate national guidelines, care programs and the national cancer registry.

Each regional structure comprises one or two university hospitals, all with an oncology department for medical oncology and radiotherapy. Additionally, in five regions some county hospitals have oncology service, including radiotherapy. In all hospitals oncology rely on diagnostic radiology departments for diagnostic imaging. CT-scanners are available for dedicated use in radiotherapy for target delineation in treatment position.

Today, four radiotherapy departments are equipped with dedicated MR systems and at least two more are planning for installation of MR systems. At present, the role for MRI in "routine" radiotherapy is exclusively target delineation for external radiotherapy and brachytherapy. The diagnostic work-up, including diagnostic MR procedures, are performed before the patients are admitted to radiotherapy. Thus, the diagnostic and radiotherapy procedures are not in conflict but an increased flow of expertise between the disciplines would probably be mutually beneficial for the different disciplines and likely most of all for the patients.

7.2 Imaging information in radiotherapy

The use of advanced imaging for treatment planning (e.g. CT) has since a couple of decades become a routine procedure. This procedure is separated from the diagnostic work-up of most patients meaning that the diagnostic procedures are performed before treatment planning is started. The simple reason is that the diagnostic information (imaging and other) is used for treatment decision and as a background for radiotherapy treatment planning. It is also advised that the diagnostic information is updated shortly before therapy start. Generally, imaging parameters are optimized for diagnostic purposes.

In the protocols for imaging for treatment planning purposes imaging parameters are optimized differently in several aspects. Some examples are; the patients are immobilized, gantry angles are fixed, contrast agents are often not used. The scope of the imaging is usually more limited than that of a diagnostic procedure (i.e. to identify an already diagnosed tumour in relation to other structures in a new patient alignment. Thus, it is not routine to produce a diagnostic report or procedure in these cases. However, it is common to consult a diagnostic radiologist in cases where unexpected or unclear findings are suspected.

A similar approach regarding the handling of imaging information for the introduction of MRI is natural and follows already existing principles of many departments. A routine screening of images produced for radiotherapy purposes would cost valuable competence for an unknown and uncertain profit in terms of improved therapy. It should be emphasized that a close collaboration between diagnostic radiology specialists and radiation oncologists is of great importance in establishing the routines concerning both safety and optimization of image quality related to the clinical problem. This collaboration should also be extended to interdisciplinary discussions concerning different areas of imaging and special cases as well as educational aspects of MRI based target volume delineation.

In general, similar principles should be adopted with the introduction of MRI. It is of importance that patients are informed about the difference between a diagnostic and a treatment planning investigation in order to prevent unrealistic expectations. A similar policy may guide imaging performed exclusively for research purposes.

7.3 Future development of MR in radiotherapy

7.3.1 Positioning, treatment planning and dose calculation

The second objective for dedicated MR-equipment for radiotherapy is research and development. In the basic set-up MRI is used for definition of anatomy. MR-Images are registered with CT images and the dose calculation and treatment planning is based on CT. It is well known that MR-CT registration introduces systematic errors that may be significant (1,2). In order to eliminate this source of error an “MR-only” based alternative work flow needs to be implemented. A number of measures are needed to be taken before such a work-flow may be realized e.g.

- A QA procedure with respect to errors introduced by MR such as geometrical uncertainties etc.
- Segmentation (automatic) of bone and air for dose calculation and for production of substitute for DRR for verification purposes.
- 4-D MR studies for defining organ motion and possibly tracking.
- Finding methods for optimizing images under radiotherapy conditions and demands such as, fixations/immobilisations, coil arrangements and sequences.

7.3.2 Previous and ongoing studies

MRI offers a wider range of opportunities to exploit functional tissue information than CT. This is a rapidly expanding area of research. Information about the tumour may be assessed pre-treatment and in conjunction with a radiotherapy course during several weeks. It is assumed that therapy may still be modified in order to increase the probability of an adequate treatment effect. Such measures may consist of local radiation boost and/or the addition of anticancer drugs. None of these potentially beneficial treatment modifications have yet been introduced into general clinical practice but subjected to ongoing research. Functional MRI for assessment of treatment response in cancer is a rapidly expanding area of research. Despite increasing knowledge about factors determining treatment effects in cancer there are few examples where treatments are truly personalised.

In cancer radiotherapy, treatment is frequently administered during an extended time period. Today the evaluation of the effectiveness usually takes place, at least, a couple of months after start of therapy. One reason is that the ”early” evaluation of tumour response for most cancers is limited to measurement of the tumour contours by radiological methods. The results given by such end-points will not be able to discriminate between different patterns of response such as differential responses within the tumour. Furthermore, the time between therapy and evaluation often comprises the therapeutic interval in which there still exists a possibility to adapt or completely change a suboptimal therapy.

Detection of early response predictors or, monitoring of effect, will be an important adjunct to further development of cancer therapy. There are many examples of early changes that are predictive for outcome.

E.g. changes in metabolism measured by FDG-PET and labelling index by infusion of halogenated pyrimidines in vivo have both shown a strong predictive capacity as early as one week into a 6-7 weeks treatment for head and neck cancer (3,4). It is noteworthy that similar results arise from studies of completely different processes. These observations together with later observations in other cases such as cervical cancer (5) and glioma (6) support the hypothesis that treatment effects give rise to complex responses in different cellular processes. They may be identified by a number of methods and combining different methods is likely to be an effective way to move forward. In the present literature usually one or a few imaging biomarkers have been analysed in small patient populations (5,7). They have rarely been further validated and thus, established as a basis of clinical decision-making. One probable reason is that few single markers are able to reflect the complexity and the heterogeneity of human tumours (8,9). The need for use of multiple imaging biomarkers is challenged against the need for standardised procedures and protocols.

A number of ongoing studies with such aims are presently being conducted in Europe and the USA. Through a search (23 Dec 2013) at ClincalTrials (www.clinicaltrials.gov), using the criteria radiotherapy+response+MRI, adaptive+radiotherapy+MRI and radiotherapy+dose-painting+MRI, 50 studies were identified. Studies relevant for evaluating response in the early phases of external beam radiotherapy or for guiding of treatment were selected. Six studies concern the early response or for guidance of therapy in prostate cancer, four studies of brain tumours, three studies of head and neck cancer and one concerning rectal cancer and hepatocellular carcinoma respectively were found. In most trials several techniques were used in a multiparametric approach (DCE, DW-MRI and in some MRS). A large proportion of studies also comprise PET-studies. It is likely that a more comprehensive search would have identified several more similar studies since the nomenclature is not strictly defined. The large number of ongoing studies indicates that there is a large interest in this topic and an increasing hope for a more personalised radiotherapy. Most of the studies are focused on finding predictors of tumour response. So far only two on-going studies have used MRI data for defining volumes of interest for e.g. boost treatment/dose-painting (10).

7.3.3 Need for clinical studies

In order to realize MR implementation in clinical radiotherapy as outlined above well planned clinical studies are needed. Multi-centre studies will be required for time effective research, sufficient patient numbers and generalizability. Several lines of studies directed towards specified aims need to be performed:

Comprehensive studies are required to identify parameters with potential predictive information at start of therapy and during the first two weeks of therapy. A long-term follow up of these patients is also needed in order to establish the effect on important outcome measures such as loco-regional control and survival. The evaluation of the vast amount of data needs specialized statistical expertise.

The next phase of studies are even more important since predictive parameters need to be met with some therapeutic measures to compensate for e.g. poor response. Many reports of predictive biomarkers end with a statement that "further studies are required". Only rarely studies validating the predictive power of the markers are reported. It is therefore of importance that strategies for identifying markers of response include a validation process. Finally the establishing of methods for use in clinical routine will often demand full, randomised controlled trials. However, in case of the finding of strongly predictive parameters for outcome, the number of patients needed to answer the question should be moderate.

7.4 Summary

In order to build a solid base of knowledge, the ongoing studies will not suffice. More data under different conditions and during different kind of treatments need to be collected to establish any indicators of response or insufficient response that may be used in clinical trials. One major obstacle is the vast amount of data from each patient who undergoes a series of functional imaging sessions. The preparation and handling of data will demand a solid research infrastructure with specialists from different disciplines. Most radiotherapy centres presently lack this infrastructure. The increasing number of MR-scanners at radiotherapy departments will facilitate the forming of such structures. This challenge has to be considered at both at hospital administrative and research administrative level to organize an infrastructure that clearly promotes collaborative efforts between disciplines within each radiotherapy department, in this case especially radiation oncology, hospital physics and diagnostic radiology. For a small country with limited regional resources a joint effort between several hospitals might be a possibility to gather the resources needed.

7.5 References

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8. Summary and recommendations

8.1 Summary

Due to its superior soft tissue contrast MRI is of importance in identifying tumours and critical normal tissues in several tumour sites such as, pelvis, brain and head and neck regions. However, CT-data is still the basis for dose calculations. Today the common method for using MRI requires CT data for registration, which introduces uncertainties. An MRI-only approach to treatment planning has been proposed in order to avoid the uncertainties associated with image co-registration. This means that dose-calculations need to be performed by using synthetic CT, derived from MR information. In order to avoid co-registration uncertainties, voxel-based synthetic CT is an attractive approach. The associated dosimetric uncertainty should be minute. Ongoing work aims to further improve the accuracy and applicability of these methods. Although there are certain remaining issues with regard to MRI-based treatment planning and absorbed dose calculations, practical solutions are well within reach.

The introduction of MRI (only or in combination with CT) in radiotherapy requires procedures that are specific for this purpose. MRI is prone to geometrical distortions, which have to be controlled. The scanning procedure should be optimised and, as far as possible, standardised for its purpose. Safety issues need to be addressed. Fiducial markers need to be MR-compatible and verified concerning production of artefacts. MR-derived synthetic CT must be validated both as a basis for dose calculation and geometric accuracy for their use as DRRs for reference purposes. Methods for immobilisation need to be designed with materials that are compatible with both MR and radiotherapy. Special coil arrangements are often necessary for MRI in treatment position. Coils can usually not be placed on the skin due to distortion their weight causes the body contour. Reasonable deviations from optimal coil arrangements for image quality have to be considered due to imaging of patient in treatment position.

The role of multi-parametric MR-methods for functional imaging as a tool for characterisation of tissue and monitoring of response is not yet established. There are many indications that the information that may be assessed from such investigations could play an important role in treatment selection and adaption. More data under different conditions and during different kind of treatments need to be collected. One major obstacle is the vast amount of data from each patient who undergoes a series of functional imaging sessions. The preparation and han-

dling of data will demand a solid research infrastructure with specialists from different disciplines. Most radiotherapy centres presently lack this infrastructure. This challenge has to be considered both at hospital administrative and at research administrative level to organize an infrastructure that clearly promotes collaborative efforts between disciplines. The methods need to be clinically validated and standardized tools for acquisition and analyses are required. In the future these activities may give important information for the personalisation of radiotherapy. This is a growing area of research. Due to the potential benefits for patients receiving radiotherapy it is important that the competence in Sweden is built in parallel to international efforts. Therefore this area of research is recommended a high priority for research support.

When applying MR-technology in radiotherapy it remains evident that the development involves several disciplines. Classic diagnostic radiology is in all cases assumed to be separated from MRI in radiotherapy. Diagnostic work-up of the patients is performed before entering the therapy process and imaging. Radiotherapy imaging is an entity with other goals for optimising of procedures. Thus, the procedures should be kept apart as in the case of conventional CT-based radiotherapy. However, we are firmly convinced that a close collaboration between radiologists, radiation oncologists and medical physicists is a prerequisite for a successful use of advanced imaging in radiotherapy. To translate the complex image data into a clinical decision process it is also likely that more specialists will need to contribute e.g. statisticians, molecular pathologists etc.

8.2 Recommendations

It is the view of this group that MRI in radiotherapy is a new and promising area of clinical development that aims to further optimise the radiotherapy on an individual level. For exploiting the potential benefits more research is needed in conjunction with development of competence. In the present report we have reviewed the field and identified several aspects that should be addressed with a high priority:

1. The standardisation of imaging procedures and quality assurance processes of MRI for radiotherapy is needed for safe introduction of MRI in radiotherapy:
    a. As a tool for target localization and definition
    b. As a basis for dose calculation
    c. As a reference for positioning and in the future, possibly tracking

2. Comprehensive research efforts are needed for the exploring and validating of multi-parametric imaging data for personalised radiotherapy.
    a. Support for clinical studies for assessing data
    b. Core facilities for data handling, post processing and analyses of data
    c. Clinical studies for utilising the new knowledge

The introduction of MRI represents an important step in the evolution of clinical radiotherapy. This step holds great promise for improved future treatments and research. It requires an active involvement of the entire community associated with radiotherapy including authorities, research funds, radiotherapy departments and universities involved in the education of professionals in radiotherapy. The efforts must strive to assure requirements for education, research and staffing in order to ensure a safe implementation of the new technology. Direct access of dedicated MR scanners at all radiotherapy departments is fundamental and requires active involvement of the health care system to provide the equipment needed. The implementation of MRI in radiotherapy also requires an active involvement of care programme groups and sponsors of clinical radiotherapy studies to describe the use of MRI in oncology in a structured way. An active participation in international radiotherapy communities is important to facilitate standardisation of MRI protocols in radiotherapy. National clinical studies should be encouraged and supported by the formation of appropriate quality- and research registries capable of harbouring large quantities of data including image data. The implementation of MRI in radiotherapy obviously requires increased efforts and resources for clinical radiotherapy research and development. To optimize the allocation of research resources, a mapping of current radiotherapy research must be conducted in order to identify bottle-necks for the development of Swedish radiotherapy research.

In conclusion: Following the roadmap outlined above, a successful implementation of advanced MRI methods in radiotherapy will be possible and result in a step towards personalised radiotherapy between several hospitals might be a possibility to gather the resources needed.



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The Swedish Radiation Safety Authority has a comprehensive responsibility to ensure that society is safe from the effects of radiation. The Authority works to achieve radiation safety in a number of areas: nuclear power, medical care as well as commercial products and services. The Authority also works to achieve protection from natural radiation and to increase the level of radiation safety internationally.

The Swedish Radiation Safety Authority works proactively and preventively to protect people and the environment from the harmful effects of radiation, now and in the future. The Authority issues regulations and supervises compliance, while also supporting research, providing training and information, and issuing advice. Often, activities involving radiation require licences issued by the Authority. The Swedish Radiation Safety Authority maintains emergency preparedness around the clock with the aim of limiting the aftermath of radiation accidents and the unintentional spreading of radioactive substances. The Authority participates in international co-operation in order to promote radiation safety and finances projects aiming to raise the level of radiation safety in certain Eastern European countries.

The Authority reports to the Ministry of the Environment and has around 315 employees with competencies in the fields of engineering, natural and behavioural sciences, law, economics and communications. We have received quality, environmental and working environment certification.

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