This is an author produced version of an article that appears in:

CURRENT MEDICAL IMAGING REVIEWS

The internet address for this paper is:

https://publications.icr.ac.uk/7438/

Published text:


Institute of Cancer Research Repository
https://publications.icr.ac.uk

Please direct all emails to:
publications@icr.ac.uk
Applications of Computed Tomography, Magnetic Resonance Imaging and Magnetic Resonance Spectroscopy for Planning External Beam Radiotherapy

Geoffrey S Payne¹,*, Elizabeth Charles-Edwards¹ and Christopher P South²

¹Cancer Research UK Clinical Magnetic Resonance Research Group and ²Radiotherapy Physics Department, Royal Marsden Hospital and the Institute of Cancer Research, Downs Road, Sutton, Surrey, SM2 5PT, UK

Abstract: In this educational review the relative merits and current status of computed tomography (CT), magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) in the planning of radiotherapy are discussed. Following a general introduction to the requirements of medical imaging in this context each imaging modality is described in turn. Computed tomography is by far the most widely used, being fast, geometrically precise and providing the electron density information required for dose calculations. Historically MRI has been little used owing to the presence of geometric distortions and lack of electron density information. However the superior tissue contrast to CT has stimulated strategies to overcome these limitations. Co-registration to CT images solves both problems but is non-trivial and requires both sets of exams to be performed. Alternatively methods are available to correct distortions and to segment images to make good estimates of electron density. Magnetic Resonance Spectroscopy probes tissue biochemistry, showing good contrast between tissues, and showing treatment response sooner than other modalities. However spatial resolution is poor (~1cm) and the method can be slow. Spectra are intrinsically co-registered to MR images acquired in the same examination, but require the same corrections for geometry and electron density information as MRI.

Keywords: Radiotherapy; planning; computed tomography, magnetic resonance imaging; magnetic resonance spectroscopy; registration.

The last few years have seen substantial developments in the technologies of medical imaging, radiotherapy planning and radiotherapy delivery. In this review we summarize some of these developments, and discuss different contributions of computed tomography (CT), magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) to radiotherapy planning.

Radiotherapy, the treatment of a medical condition using ionizing radiation, is used almost exclusively in the treatment of malignant cancers, where the aim is to preferentially kill tumor cells whilst minimizing the damage to surrounding normal tissue. This requires the radiation to be accurately targeted to the disease site. Both the radiation dose and delivery schedule must be carefully chosen depending on both the clinical objective (curative or palliative) and the delivery technique.

When a cell is damaged by ionizing radiation, three outcomes are possible: the damage may be accurately repaired, resulting in no overall change in cell function; the cell may be incompletely or inaccurately repaired, resulting in a modification of the cell, which can, in turn, lead to a malignancy or hereditary disorder; or the cell may be unable to repair itself, resulting in cell death. In normal tissue a proportion of cells may be killed without a noticeable change in tissue function. However, above some threshold level of cell kill, the tissue or organ function will begin to be compromised, resulting in toxicity or even death. Radiotherapy is a feasible treatment option only in cases where doses to the tumor are high enough to give a significant probability of achieving the therapeutic aim (shrinkage or elimination of the tumor) without resulting in excessive normal tissue damage.

The radiation dose may be delivered using external beam radiotherapy, in which one or more beams of radiation from an external source are directed through the patient, targeting the tumor region; or using brachytherapy, in which a number of radioactive sources are placed in or near the tumor. An additional technique, known as unsealed source therapy, involves labeling a tumor-targeting drug with a radioactive isotope and delivering this radioactive drug systemically, or injecting a radioactive compound directly into the disease site. In many ways, this technique can be considered a form of brachytherapy. It is estimated that worldwide ~50% of cancer sufferers either receive or would benefit from radiotherapy as part of their treatment, and that radiotherapy is directly responsible for at least 40% of patients surviving beyond 5 years [1].

EXTERNAL-BEAM RADIOThERAPY

In External Beam Radiotherapy (EBRT) an X-ray generator, particle accelerator, or radioactive source is used to produce an intense beam of radiation, the size, shape, and direction of which can be tailored to target the tumor. The energy and type of radiation used will depend on the location of the tumor and the equipment available. For superficial tumors, the radiation is not required to penetrate deeply into tissue, so relatively low energies can be used. Photon beams with energies up to ~300 keV can be produced using conventional X-ray generators, and these are still used to treat...
many superficial lesions. A significantly higher energy can be achieved by using radioactive $^{60}$Co as the source of a photon beam. The radioactive decay of $^{60}$Co produces gamma rays with a mean photon energy of a little over 1 MeV. The use of cobalt treatment units has declined significantly in recent years, though they are still widely used in many centers worldwide. However, modern radiotherapy is most commonly delivered using a linear accelerator, a device capable of producing a beam of either photons or electrons with energies up to ~25 MeV. Larger particle accelerators can also be used to produce beams of high-energy protons or heavier ions for radiotherapy, but their use is not widespread due to the size and cost of the equipment.

**THE ROLE OF IMAGING IN TREATMENT PLANNING**

In radiotherapy medical imaging is required for planning the treatment, for verifying that the delivered treatment is consistent with the planned treatment, and for assessing and monitoring the response to treatment. The aim of treatment planning is to use all available information to ensure that the disease site receives a sufficient dose to give a reasonable probability of achieving the clinical objective, whilst minimizing the damage to surrounding normal tissue. For kilovoltage photon treatments and for electron beams this is generally a simple process involving choosing the position, shape, size, and energy of a single beam and calculating the delivered dose. For these types of treatment the key decisions can be made with relatively little information and little or no imaging is required. However, for megavoltage photon treatments several beams are generally configured in such a way that they enter the patient from different directions and overlap in the region of the disease site. In this case, in addition to choosing the position, shape, size, and energy for each beam, the number and relative weighting of beams must also be determined in order to optimize the planned distribution of dose. The choices made at this stage will largely determine the quality of the delivered treatment, so it is important to ensure that there is sufficient information available on the location and extent of disease and the relative position of organs at risk. Where 3D image data are used for this purpose, the images must be passed from the scanner to a specialized treatment planning system (TPS), which allows them to be used to delineate structures of interest, design a treatment plan and calculate the resulting dose distribution. It is important to ensure that the data transfer process does not cause any alteration to image scaling, orientation or voxel values.

A number of useful concepts regarding targeted disease and surrounding normal structures are defined by the International Commission of Radiation Units and Measurements [2]: the Gross Tumor Volume (GTV) is the “gross palpable or visible/demonstrable extent and location of the malignant growth”; the Clinical Target Volume (CTV) is the “tissue volume that contains a GTV and/or subclinical microscopic malignant disease, which has to be eliminated”; the Planning Target Volume (PTV) is “a geometrical concept, and is defined to select appropriate beam size and beam arrangement, taking into consideration the net effect of all the possible geometrical variations and inaccuracies in order to ensure that the prescribed dose is actually absorbed in the CTV”;

and Organs at Risk (OARs) are “normal tissues whose radiation sensitivity may significantly influence treatment planning and/or prescribed dose”. The CTV is therefore the anatomical region to be treated, and the PTV is constructed from the CTV allowing sufficient margins to account for any variations between planning and treatment (including errors in repositioning the patient and internal organ motion) and for any uncertainties in determining the extent of the CTV. This last uncertainty will be largely determined by the quality of the imaging available for treatment planning. The larger the sum of these uncertainties, the larger the margin required to construct the PTV and consequently the larger the irradiated volume. Minimizing these uncertainties will therefore minimize the volume of normal tissue treated, and in particular help to reduce dose to OARs close to the CTV. Fig. (1a) shows a typical GTV, CTV, and PTV, outlined using a combination of CT and MRI; the corresponding radiotherapy dose distribution is shown in Fig. (1b).

Historically, radiotherapy was planned by calculating the dose distribution in a single plane through the center of the target volume and this was taken to be representative of the treatment as a whole. A single outline of the patient would be acquired and the position of targets and OARs would be estimated from planar X-ray images. Simple, often rectangular, fields would then be designed to cover the PTV, and the dose distribution would be calculated assuming the patient density to be uniform. However, the increased availability of 3D X-ray CT imaging and the development of treatment planning software to calculate dose distributions in 3D based on these images have led to fully 3-dimensional treatment planning becoming the standard approach for most treatments, particularly those with curative intent. 3D imaging allows a full picture of the size, shape, and relative position of targets and OARs to be acquired, so that a plan can be optimized bearing in mind the full dose distribution, and doses to each important structure can be analyzed. Beams can be shaped to irradiate only the PTV, shielding surrounding normal tissue, particularly any OARs close to the target. It is also possible to plan simple treatments using traditional 2D planning methods based on a 3D image set, a process known as Virtual Simulation. The 3D data are used to create 2D planar images known as Digitally Reconstructed Radiographs (DRRs), which are used to determine the position, size, and shape of the treatment field or fields.

In addition, modern 3D dose calculation algorithms can account for variations in both scattering and absorption of radiation by different types of tissue, so that variations in electron density within the patient can be determined; this information can be used to calculate the dose distribution with greater accuracy. Therefore, the ideal imaging technique for radiotherapy planning would provide sufficient resolution and contrast to allow both the differentiation of malignant and normal tissue and precise outlining of OARs, and also provide accurate data on variations in density within the patient.

A significant development in radiotherapy in recent years has been the widespread clinical implementation of Intensity Modulated Radiation Therapy (IMRT). This is a further refinement of conformal radiotherapy in which not only is each beam shaped to the PTV, but the radiation fluence is
also varied across each beam such that different regions of the beam deliver different amounts of dose, giving greatly improved flexibility in the spatial distribution of delivered dose. This can be done either by breaking each beam down into a number of different shaped segments to be delivered sequentially or by dynamically changing the size and shape of the beam during delivery [3]. IMRT has generally been used to improve the conformity of a high-dose region to the PTV, particularly for complex geometries where the PTV forms a concavity containing an OAR. However, the technique has the potential to deliver complex non-uniform dose distributions designed to account for spatial variations in tumor burden and radio-sensitivity within the target volume, if accurate information on such heterogeneities and their effect on radiation response were available [4].

PATIENT POSITIONING

It is crucial to the treatment planning process that the images used are an accurate representation of the patient at the time of treatment. In practice this is impossible, because we cannot image, plan, and treat instantaneously, so any potential variations between imaging and treating must be minimized and residual uncertainties accounted for in the PTV margin. The positioning of the patient must therefore be made as reproducible as possible, and the position of the patient during imaging must match the treatment position as closely as possible. Variations in patient set-up at treatment are minimized by positioning the patient on a hard, flat-topped couch, and a variety of fixation devices can be used to immobilize the patient, ranging from knee supports and ankle stocks for pelvic treatments to fitted thermoplastic shells or fixed stereotactic frames for treatments in the head and neck. Some customization is often still necessary to allow replication of a treatment position on a diagnostic scanner, because these are generally not provided with a flat couch top capable of locating a range of immobilization devices, or with fixed lasers to align external marks on the patient. There can also be physical limitations of the scanner, such as the bore size, which prevents patients being imaged in certain positions. It is advisable to involve radiographers with therapy experience at the scanning stage when acquiring images for treatment planning, as they will appreciate the importance of issues regarding patient positioning.

MOTION ISSUES

Even if the patient treatment position is carefully replicated during scanning, planning images will never be a perfect representation of the patient due to organ motion both between and during scanning and treatment. The relative positions of organs can be affected by breathing, cardiac motion, and changes in bladder and bowel filling. For the latter, attempts are usually made to standardize the condition of bladder and bowel both for imaging and treatment. For more predictable periodic motions there are a number of

Fig. (1a). shows GTV(red), CTV(yellow) and PTV(purple) on CT (left) and MRI (right) images respectively. Fig. (1b) shows a typical radiotherapy dose distribution with the 95% isodose (green) covering the PTV(purple).
different approaches that can be taken to deal with this issue. The simplest approach is to assume that if the scan acquisition time is long compared to the timescale of the motion of interest, the image will indicate the range of motion and approximate average position of the organ in question. However, the validity of this assumption depends very much on the particular image acquisition process, and the type, and severity of imaging artefacts due to organ motion will depend on the imaging technique used. A second approach is to effectively freeze the motion at a single point in the cycle. This can be done either literally, for example, by imaging and treating during a breath hold, or virtually by gating both image acquisition and treatment to occur at a fixed point in the cycle. Finally, a more accurate representation of how the position of each organ varies with time can be built up by acquiring separate image sets for a number of different phases of the cycle, either by gating at multiple points in the cycle or by labeling acquired image data with the phase at which it was acquired and retrospectively rebinning into the required number of phases. This approach is known as 4D imaging, and can be used to customize PTV margins based on the known amplitude of CTV motion for a given patient [5].

MULTI-MODALITY IMAGING AND IMAGE FUSION

No ideal imaging technique exists which provides optimal contrast and resolution in addition to electron density data (required for the computation of energy deposition by the irradiating beams). In many cases a suitable compromise can be found and a single imaging modality chosen for treatment planning. In some situations, however, it is desirable to combine information from two or more imaging modalities in order to allow both precise outlining of important structures and accurate calculation of the dose distribution. This may involve combining complementary morphological information from CT, MRI, and ultrasound, or supplementing anatomical images with physiological data from Positron Emission Tomography (PET), Single Photon Emission Computed Tomography (SPECT), or Magnetic Resonance Spectroscopy (MRS).

Patient positioning issues become particularly important where multi-modality imaging is used, since the patient set-up must be replicated at each imaging session. The two or more image sets must then be co-registered to ensure that anatomical features coincide as closely as possible. A variety of techniques are available for matching data sets from multiple scans, ranging from simple manual matching to sophisticated automated techniques. Point-based techniques involve the matching of a number of fixed points, which may be markers placed on the patient during each scan, or easily identifiable anatomical landmarks chosen to be clearly visible for all modalities. Voxel-based techniques automatically match images by adjusting the relative positions of the scans to maximize the correlation between coincident voxel values in the two data sets. These methods are only appropriate where contrast mechanisms are such that there is a reasonably linear (or inverse) relationship between voxel values in similar tissues for the two modalities. Where this is not the case, mutual information algorithms, which maximize the information shared between two data sets, are more robust [6]. If patient position is known to have varied between two scans it may be necessary to optimize the image match over a limited sub-volume including only the structures which the secondary scan will be used to outline. The problem of image registration is largely removed in situations where two complementary image sets can be acquired in a single imaging session on the same scanner such that the data are inherently co-registered (such as in combined PET/CT systems).

It is important to know the precision with which any two scans can be registered as errors in the matching (including those due to genuine differences in patient position or changes in anatomy between scans) will contribute to the overall uncertainty in defining the CTV and should therefore be accounted for when assigning a PTV margin [7]. Multimodality imaging will only be useful in situations where the improvement in the precision of outlining key structures due to improved contrast or resolution in the secondary image set is greater than the uncertainty in registering images.

ROLE OF IMAGING IN TREATMENT VERIFICATION

The second major role of imaging in radiotherapy is to help ensure that the delivered treatment matches the planned treatment as closely as possible. This involves verifying that the patient is set up in the planned position, and that the treatment fields are correctly aligned with the patient such that the high dose region coincides with the CTV. The patient is initially positioned on the treatment machine using tattoos on the patient’s skin, or marks on a fitted immobilization device, placed at the time of the planning scan. The simplest way to verify patient position relative to a linear accelerator is to acquire two orthogonal planar images of the patient using the treatment beam. Images were traditionally acquired using film, but most modern linear accelerators are fitted with an imaging panel known as an electronic portal imaging device (EPID). These images can then be compared to DRRs generated from the planning scan in order to quantify any shifts from the planned position in terms of linear translations along 3 orthogonal axes. Megavoltage imaging suffers from poor contrast, and soft tissue is not well visualized, so image matching is most often carried out using bony landmarks. However, some organs may move significantly relative to surrounding bone, so for some treatments it is beneficial to insert high-contrast markers such as implanted gold grains in or close to the target and match EPID images to DRRs using these markers. Verification images are typically acquired periodically during the course of treatment, enabling the identification and correction of systematic errors as well as the quantification of random errors. Information on the magnitude of these errors can then be used to ensure that appropriate margins are being used in defining PTVs for a given treatment site [8].

It is becoming increasingly common for linear accelerators to be fitted with a secondary kilovoltage X-ray source to enable diagnostic quality planar images or even cone-beam CT to be acquired with the patient in situ. Registration of a CT scan acquired at treatment with the primary planning scan allows assessment of both rotational and translational errors in patient positioning, although the best strategy for utilizing this information is still under investigation.
**COMPUTED TOMOGRAPHY IMAGING AND RADIOTHERAPY**

Principles of Computed Tomography

Computed Tomography uses X-rays to acquire 3D image data of a patient with contrast between tissues of different density. Photons passing through any material will be attenuated, and the attenuating properties of a particular material can be described by defining the reduction in intensity of a photon beam of a given energy per unit distance traveled in the material. This property is known as the linear attenuation coefficient, \( \mu \), of the material. In conventional planar X-ray imaging, a beam of photons travels from an approximate point source through the patient to an array of detectors or a film. The image produced is a 2-dimensional representation of the 3-dimensional variation of \( \mu \) within the patient. The fraction of photons reaching a given point at the detector depends on the path length through the patient along the line projected back to the radiation source, and on the attenuating properties of the tissue at each point along that line. By obtaining a large number of projection images at different angles through the patient, it is possible to deduce the 3D distribution of linear attenuation coefficients within the patient. A CT scanner therefore consists of an X-ray source with an opposing detector array configured such that the source can rotate about the patient producing projection images at each angle.

There are two main classes of algorithm for creating 3D image sets from the raw projection data. Back-projection methods involve effectively reversing the data acquisition process. The intensity measured at each detector position for a given projection is assigned to all voxels along the line of sight from the source to that detector element. This is carried out for each detector element for each projection and the result is summed to produce an image. Some blurring of features is inherent in this reconstruction method, but this can be minimized by filtering the projection data to remove high spatial frequencies prior to reconstruction, a technique known as filtered back-projection. The second class of reconstruction algorithms contains the iterative or forward-projection methods. These involve beginning with an assumed 3D distribution of \( \mu \) and calculating the expected planar projection images for this distribution. The predicted projections are then compared with the observed projection images and the \( \mu \) distribution is iteratively adjusted to optimize the match between the two. In clinical practice filtered back-projection methods have generally been used because they are much less computationally intensive and therefore offer much shorter reconstruction times.

The initial result of reconstruction is an image showing the variation of \( \mu \) within the patient. However, this is usually rescaled to give each voxel a “CT Number” describing its attenuation relative to the attenuation of water, given by:

\[
CT\ Number = \left( \frac{\mu - \mu_{\text{water}}}{\mu_{\text{water}} - \mu_{\text{air}}} \right) \times 1000 \quad [1]
\]

A positive CT number therefore indicates that a tissue is more attenuating than water, while tissues with a lower density than water have a negative value. CT numbers are expressed in “Hounsfield Units”, named after the inventor of the first clinical CT scanner, which was designed by Godfrey Hounsfield and built by EMI in 1971 [9].

Scanner Design

The first clinical CT scanner was designed solely for cranial imaging and had a single X-ray source collimated to a narrow pencil beam directed onto two detectors, allowing the acquisition of two slices for each rotation. Both the source and the detectors tracked linearly across the field of view before rotating round to the next projection angle. Projections were acquired at 1° intervals from 0° to 180°, allowing reconstruction of a 3D image set with resolution of 3 mm within the plane of each slice and with a slice thickness of 13 mm.

A number of modifications were made to the fundamental design of CT scanners over the course of the following decade in order to address some of the limitations of the first scanner by reducing scan times and increasing the field of view. The so-called “second generation” scanner used a fan-beam X-ray source with an arc of detectors allowing numerous projections to be acquired simultaneously for each linear scan; thus, reducing scan times dramatically. In “third generation” scanners, the fan-beam was widened further to cover the whole cross-section of the patient with an even larger number of detectors used. The most fundamental change, however, was to eliminate the linear motion of source and detectors, which instead were allowed to simply rotate through 360° about a fixed circle. The divergent geometry of the fan beam increased the complexity of the image reconstruction process, but the scanning time was again dramatically reduced. Finally, “fourth generation” scanners utilized an entire ring of detectors encircling the patient, so that only the X-ray source needed to rotate about the patient. This approach allows the fast acquisition of high-resolution data, but the large number of detectors required results in high manufacturing costs, and geometrical issues cause an increase in image noise due to scattered radiation. Most modern CT scanners are based on the third generation design, with images reconstructed by re-binning divergent fan beam projection data from different source angles into sets of parallel ray lines before applying a filtered back-projection method.

Further refinements to this basic design have occurred during the intervening decades. Slip ring technology, developed around 1990, allowed the continuous rotation of the gantry, bringing slice acquisition times down to as low as 0.3 sec. At the same time helical scanning was introduced, which combined continuous rotation with continuous longitudinal motion of the patient, such that the acquired projection data form a helical path through the patient. This means that no two projections are in precisely the same plane, so the projection data must then be interpolated prior to reconstruction in order to produce a set of transaxial slices. This results in a slight broadening of the effective slice profile. However it has the advantages of increased scan speed and flexibility of reconstruction, because the position of the slices, and interval between them, can be chosen retrospectively. Scan times have since been further reduced by the development of multi-slice CT scanners, which use a 2D array of detectors to acquire a number of slices (or indeed helices) simultaneously. This allows shorter scan times,
larger scan volumes or finer longitudinal resolution. However, if more than 8 slices are acquired simultaneously, the out-of-plane divergence of the fan beam becomes significant, and this further complicates the image reconstruction process and requires greater computational power to generate the image set.

Another innovation of particular relevance to radiotherapy is the introduction of wide-bore CT scanners. A standard CT scanner typically has a bore diameter of ~70 cm, with a field of view of 50 cm. The bore size can limit patient positioning in some circumstances, particularly where it is necessary to raise the arms of the patient away from the treatment area. Also, unusually large patients may extend outside the field of view, causing artifacts and loss of data which must be accounted for in the dose calculation for any treatment beam passing through the affected region. Wide bore scanners are now available with a gantry aperture of up to 90 cm, with a field of view up to 70 cm (or even 85 cm using extended reconstruction methods with reduced numbers of projections at the extremities). A fundamental limitation of CT imaging is that it provides only anatomical, not physiological information. However, the development of Dynamic Contrast-Enhanced CT (DCE-CT), in which multiple scans are acquired sequentially following the administration of a contrast agent targeting the organ or disease of interest, allows some functional information to be obtained. However, the radiation dose during such measurements can be significant.

**Image Quality**

Computed tomography image quality depends on a large number of parameters particular to the scanner and the imaging protocol in question, including tube voltage, tube current, focal spot size, scan time, slice width, helical pitch, collimation of the beam and/or detectors and the interpolation and reconstruction algorithms chosen. However, the values in Table 1 represent those typically achievable using a modern 16-slice scanner. The Modulation Transfer Function (MTF) describes the contrast of an imaging system as a function of spatial frequency, where for example the MTF50 is the spatial frequency at which the contrast drops to 50% of the value seen at low frequencies.

### Table 1. Computerized Tomography Quality Parameters Typically Achievable Using a Modern 16-slice Scanner (Defined by the Modulation Transfer Function, MTF, in Line-Pairs Per cm)

<table>
<thead>
<tr>
<th>Limiting in-plane resolution</th>
<th>MTF50 [lp/cm]</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MTF10 [lp/cm]</td>
<td>16</td>
</tr>
<tr>
<td>Limiting z-axis resolution</td>
<td>MTF50 [lp/cm]</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>MTF10 [lp/cm]</td>
<td>11</td>
</tr>
<tr>
<td>Low contrast resolution</td>
<td>Smallest feature discernable @ 0.3% contrast [mm]</td>
<td>5</td>
</tr>
</tbody>
</table>

**Advantages of CT Imaging for Radiotherapy**

Computed tomography has historically had excellent resolution within the transaxial plane, with rather poor longitudinal resolution due to large slice thicknesses. However, the development of helical and multi-slice scanning has allowed slice thickness to be progressively reduced, and modern scanners are capable of producing approximately isotropic 3D image data with voxel dimensions of ~1 mm. Even high resolution images can be acquired remarkably quickly using multiple-slice scanners, with the time taken to scan and reconstruct 30 slices as low as 5 sec on some scanners.

The major advantage of CT imaging for radiotherapy planning is the relationship between the measured quantity, linear attenuation co-efficient, and the electron density data required for accurate dose calculations. It is simple to generate a calibration curve relating the two quantities for a given scanner and tube voltage by imaging a phantom containing a number of different materials with known electron densities. This calibration curve then enables treatment planning software to perform the conversion from μ to electron density when calculating the dose deposited by a treatment beam, or simulating planar imaging through the data set to create DRRs. When combined with the wide availability and relatively low running costs of a CT scanner, this has led to CT being the modality of choice for 3D treatment planning.

**Limitations of CT Imaging for Radiotherapy**

Whilst contrast in CT using appropriate windowing is adequate to outline many structures of interest, there are some organs, such as the prostate, where boundaries are difficult to visualize. For many disease sites it can also be difficult or impossible to differentiate between tumors and surrounding normal tissue. In these situations it is often necessary to use other imaging techniques to provide either anatomical imaging with improved contrast or physiological imaging to indicate the location and extent of disease.

Computed tomography image data are prone to a number of different types of image artifact which may affect both the precision of outlining structures and the accuracy of dose calculations. In particular, any unusually high-density material within the field of view, such as dental fillings or metal prosthetic implants, causes a combination of high-intensity streaking and low-intensity shadowing of adjacent structures. Techniques are being developed to suppress these types of artifacts during image reconstruction, or alternatively it is possible to extend the CT number calibration range of some scanners in order to assign accurate CT numbers to metals. It is also possible to minimize their impact on treatment planning, for example, by outlining regions which clearly have artificially high or low intensity and over-riding the density for these regions in the planning system with an estimated value. However, the net result is always an increased uncertainty in both target or OAR delineation and dose estimation. Similarly, severe artifacts can be caused where the patient extends outside the field of view of the scanner, as discussed above. Partial volume effects can also occur, giving an incorrect CT number where two different densities are present within the same voxel, although these can be minimized by reducing the slice thickness. In third-generation scanners, any variation in sensitivity of a detector will result in a circular artifact appearing, indicating that a recalibration of the detector gain is necessary.
A major disadvantage of CT when compared with MR techniques is the fact that CT involves the use of ionizing radiation. The precise dose delivered to the patient will depend on the tube current and voltage, the rotation time, slice width, helical pitch, and length of the scanned volume, but a typical effective dose for a high resolution thoracic scan is ~5 mSv. When used for radiotherapy planning it is often argued that the radiation dose delivered by the CT scanner is negligible in comparison to the prescribed therapeutic radiation dose. However, it should be remembered that CT scanning deposits dose throughout the scanned volume, not only in the target volume. With modern radiotherapy techniques leading to improved long-term survival for many disease sites the possibility of this radiation dose inducing secondary malignancies must be considered. The benefit of each CT scan performed must outweigh the associated risk, and the overall dose to the patient kept as low as reasonably practicable.

**MAGNETIC RESONANCE IMAGING AND RADIOTHERAPY**

The technical imaging requirements for optimal radiotherapy planning include geometrical accuracy, clear anatomical detail, electron density information, an ability to depict physiological descriptors relevant to the delivery of radiotherapy (e.g., hypoxia and cellularity) and the capability to provide snapshot images over a period of time similar to that of a treatment session to assess or correct for the effects of tumor motion. Such images, in addition to depicting gross anatomical extent of the tumor and relative geometry of surrounding normal tissue, would enable the identification of areas of radio-resistance and potentially of dose-limiting toxicity. To appreciate the extent to which MR imaging can satisfy these criteria it is necessary to review the technology and physics of MR imaging with specific reference to its use in radiotherapy planning.

**Principles of Magnetic Resonance Imaging**

Atomic nuclei with an odd number of protons and/or an odd number of neutrons possess a magnetic dipole moment, which to some extent makes them behave like little bar magnets. When such nuclei are placed in an external magnetic field their magnetic moments or vectors align themselves with the external field just as a compass needle will align itself to the earth’s magnetic field. These nuclei also possess angular momentum that causes the nuclei’s magnetic vector to precess around the magnetic field at an angular frequency (the “Larmor frequency”) that is determined by the nuclear species (e.g., $^1$H) and by the strength of the applied magnetic field. Whilst many nuclei are ‘MR visible’ the vast majority of clinical imaging uses the most abundant isotope, $^1$H.

As a patient is moved into the bore of a scanner the randomly orientated magnetic vectors associated with the $^1$H nuclei in the body, become aligned along the direction of the applied magnetic field (generally along the bore of the MR scanner). Whilst some vectors will align themselves against the direction of the main magnetic field, a slight majority will align themselves in the slightly lower energy state associated with the direction of the main magnetic field. It is the difference between these two populations of vectors which gives rise to the equilibrium net magnetic vector with which MRI creates its images. The relative distribution of the vectors aligned with or against the main magnetic field is described by the Boltzmann distribution:

$$\frac{n_\uparrow}{n_\downarrow} = \exp \left( \frac{-\Delta E}{kT} \right), \quad \text{with} \quad \Delta E = \hbar \gamma B / 2\pi$$  \hspace{1cm} [2]

where $k$ is the Boltzmann constant, $T$ is the temperature (in Kelvin), $\hbar$ is the Plank constant, $\gamma$ is the gyromagnetic ratio of the nucleus (in rad/T/s) and $B$ is the strength of the magnetic field (in Tesla).

The signal-to-noise ratio available with MR imaging is determined by this difference in populations of the “up” and “down” magnetic moments. With an excess of only 1 out of $10^6$ at 1.5 T and $37\,^\circ C$ (body temperature) it can be appreciated that producing images with a good signal-to-noise ratio in MRI is not a simple task. In the clinical setting this can be improved in a number of ways including increasing the main magnetic field strength (i.e., a 3T machine vs. a 1.5 T), placing the coils that receive the signal as close as possible to the area being imaged and increasing the time used to complete a scan. It is worth emphasizing at this stage that whilst a CT scan takes seconds, a MRI scan of quality sufficient for radiotherapy planning may take several minutes.

To create the signal that finally produces an MR image, the net magnetic vector is tipped from its equilibrium position parallel to the main magnetic field into the orthogonal (“transverse”) plane. It is the precession of the bulk magnetic vector in this plane that induces a signal in a suitable detector coil. The ‘tipping’ is performed using a brief burst of electromagnetic radiation with a frequency bandwidth encompassing that of the Larmor frequency. At the magnetic field strengths used clinically, this radiation is in the radiofrequency range and so longitudinal magnetization is converted into transverse magnetization via a radiofrequency (RF) pulse. Once the RF pulse is switched off, the net magnetic vector returns to equilibrium by losing its transverse magnetization, approximately exponentially with a time constant $T_2$, and regaining its longitudinal magnetization with time constant $T_1$. $T_1$ and $T_2$ are both specific to the substance being imaged e.g., $T_1$ of fat is much less than that of muscle, and it is the difference in these relaxation rates that underpins the good soft tissue contrast available in MRI. The transverse relaxation rate of cortical bone, however, is so rapid that a clinical MR scanner cannot encode the signal quickly enough before it dies away completely and MR depicts cortical bone as a signal void.

**Electron-Density Information**

The nucleus-based contrast mechanism of MRI does not provide information regarding the electron density distribution of the subject being imaged; a serious drawback in radiotherapy planning where electron densities are used to predict dose distribution within the patient. This is likely to be a significant disadvantage in planning radiotherapy in regions encompassing head-and-neck, the lung and treatment through prostheses. A method of addressing this problem is to fuse MR and CT images. This fusion approach can be complicated, however, when planning treatment for prostate cancer due to variations in volume of bladder and rectum. To overcome this problem [10] planned prostate radiotherapy...
using only MR images and employing bulk assignment of electron bone density. [11] simplified the procedure further by using a homogeneous geometry in treatment planning. Dose calculations for prostate cancer and demonstrated an absolute dose agreement for the planning target volume of 2% between CT-based and MR-based IMRT plans for 15 patients and 3% between measured dose and dose predicted by the planning system. The group also successfully created MRI-derived digitally reconstructed radiographs (DRRs) by contouring relevant bony structures and assigning to them a bulk density of 2.0 g/cm³. It was stressed, however, that before MRI alone can be used for treatment planning for prostate patients, any image distortion must be quantified and corrected.

Geometric distortion in Magnetic Resonance Imaging

The method by which MR spatially encodes signal can lead to practical problems when applied to radiotherapy planning. Magnetic field gradients are applied during the imaging process which leads to a known spatial dependence of magnetic field strength, and hence of Larmor frequency, upon position. The frequency of the MRI signals detected is then used to determine their spatial origin and to reconstruct the image. Accurate spatial encoding in MRI depends on the production of a precisely specified linear variation in magnetic field across the sample during the imaging process. Discrepancies between the magnetic field experienced by the sample and that which is ‘expected’ by the reconstruction algorithm lead to image distortions.

Distortions arise from two sources: inhomogeneities in the main magnetic field (system and patient-based) and non-linearities in the applied magnetic field gradients. Non-linearities in the gradients tend to be bigger towards the edge of the field of view, and therefore are of a greater concern if MR is being used to image a relatively large field of view such as a pelvis. [12] reported that although equipped with vendor-provided gradient distortion correction software, an additional point by point correction method was necessary to reduce geometrical distortion to less than 3 mm for larger patients imaged on an open 0.23 T scanner. The effects of inhomogeneities in the main magnetic field and chemical shift effects (whereby coincident fat and water become separated in the MR image due to their slightly different Larmor frequencies) can be reduced by using strong imaging gradients and wide image bandwidths. This approach, however, causes a reduced signal-to-noise ratio. Different approaches have been used to compensate or correct for the effects of MR geometrical distortion, particularly when using large fields of view. Scanner manufacturers have provided a solution in which the magnetic field throughout the object being scanned is measured; this field map can then be compared with the expected values and the distortions calculated and corrected. Other groups have developed methods of assessing and correcting distortions independently including post-processing methods capable of removing distortion arising from both magnetic field inhomogeneities [13] and non-linearities on the gradients [14].

Conventional MR imaging offers significantly greater soft tissue contrast than that available from CT. This can enable better definition of both disease and the neighboring normal structures and organs at risk (OAR). Computed tomography image quality is reduced due to streaking artifacts associated with dental amalgam or metallic implants whilst their effect can be quite small on MRI. Inherent contrast available from T₁-weighted images can be helpful in providing good anatomical detail whilst T₂-weighted images can sensitively identify pathology. The use of 3D scanning techniques enables the reformatting of image data into any plane which can then be registered to corresponding CT images. The use of such scanning techniques also allows the implementation of surface rendering techniques which can better describe the geometrical relationships between normal and pathological structures within the body.

Patient Positioning for Radiotherapy Planning with Magnetic Resonance Imaging

Imaging patients in their treatment position requires significant changes to standard MR scanning practice. A flat top couch is almost invariably required though it may not be compatible with all types of MR scanners and will invariably lead to a reduction in bore size. Fixation devices such as those used in the treatment of head and neck cancer can prevent the use of optimally designed MR imaging coils and subsequently reduce the quality of the image. In such cases the fixation devices should be designed such that the necessary surface coils can be accommodated. It should be remembered that a MRI scan will take considerably longer to perform than a CT scan or a fraction of radiotherapy so patient comfort is an important consideration. Patient discomfort is likely to result in movement which will severely degrade the quality of the scan and a reduction in the number of patients able to tolerate the procedure. Any immobilization devices must of course be non-magnetic.

Adaptive patient positioning equipment suitable for multi-modality planning and subsequent treatment is not commonly available, and it is likely that a significant proportion will have to be made ‘in-house’. It is worth stressing that whilst carbon fiber, a common material in radiotherapy, is not ferromagnetic, it does conduct electricity and is therefore not suitable for use with MRI. Perspex equipment bolted together using brass screws will generally be MR compatible but the brass screws will cause streaking artifacts in CT imaging. In all cases a thorough evaluation of potential safety or image quality problems (e.g., potential attraction of metal components, radio frequency heating of metal, and carbon fiber components, degradation of image quality) must be achieved before products are used clinically. To reach a productive compromise between the needs of optimal MR imaging and the requirements of radiotherapy it is absolutely essential that members of both diagnostic specialties are included in the alteration to imaging/planning practice. It cannot be overemphasized that equipment and imaging techniques need to be developed synergistically with radiotherapy departments. Fig. (2) shows adaptation suitable for scanning the head and neck (Fig. (2a)) and the pelvis (Fig. (2b)).

Whilst head and neck treatment protocols benefit from interlocking fixation devices to ensure reproducible patient positioning, cancers of the prostate and rectum require the use of skin markers. The patient’s position is adjusted relative to wall mounted laser lights. Such lights, whilst necessarily present in radiotherapy planning and treatment rooms, have to be added specifically to MR scanner rooms. Due to
the necessary presence of the Faraday cage on the perimeter of the MR scan rooms, fixation of wall mounted lasers is not a simple task and are best planned and executed when the room is being built. Care must also be taken that the lasers and their power supply are MR compatible and do not present an MR safety risk in terms of ferromagnetic components or degrade the quality of the images. It is important that a system of checks and QA procedures are in place to periodically check the alignment of lasers (Fig. (2b)) and the geometric distortion associated with the MR images. Although such checks are standard procedures within radiotherapy departments, they are novel to MRI, and again discussion should take place between the specialists to produce an appropriate system of quality assurance.

Examples of Magnetic Resonance Imaging in Radiotherapy Planning

Cancer of the Brain

Thornton et al. [15] showed that addition of MRI increased the apparent macroscopic tumor volume from that seen on contrast-CT alone (although CT tumor information was also necessary) and a later study concluded that using CT alone would result in an unacceptable rate of marginal misses. A later review of CT/MR imaging vs. ante- or post-mortem neuropathological observations concluded that ~90% of the primary tumor extension is within the target volume as defined by CT (contrast-enhancing mass with a 2 cm margin) and by MRI (high signal area on T2-weighted images) [16]. The review concluded that an integrated MR/CT image should be used to delineate the CTV. [17] observed that MRI appeared to define CTVs that were larger but not inclusive of CT-defined CTVs, and advocated the use of both CT and MRI for radiotherapy planning of skull meningiomas.

In many respects the acquisition of an MR image suitable for fusing with a CT image on which radiotherapy is subsequently planned is easiest when confined to the skull. The patient is imaged in their treatment position within the CT scanner. They then have a MR scan of the brain. If the MR scan comprises a 3D volume and that can be realigned to match that of the CT, the patient does not need to maintain their treatment position in the scanner and the standard MR head coil, optimized for good signal-to-noise ratio, can be used. The concerns regarding the effects of MR distortion are lessened as the images extend over a relatively small field of view. Finally, the skull provides an excellent solid boundary at which to register the MR and CT images. Convenient as this method is however, such an approach is very much limited to tissue enclosed by the skull; for areas outside the skull, even with the use of 3D imaging, patient positioning must be identical to that used for CT imaging and for treatment.

![Fig. (2a).](left) Scanning arrangement designed for head and neck radiotherapy planning. In-house built MR compatible fixation device identical in dimensions to that used in radiotherapy enables patients to be scanned using their treatment mask and head rest. Appropriate placement of receive coils ensures images with diagnostically useful signal-to-noise ratio; use of the standard head and neck coil (insert) is not possible. Fig. (2b). (right). Scanning arrangement designed for radiotherapy planning of pelvis. A flat top couch, running the length of the MR table, is secured via a series of platforms 3cm in height, enabling coil elements to be used under the couch. The insert shows a geometry check of MR compatible wall mounted lasers.

Cancer of the Head and Neck

Evidence on the usefulness of MR in planning therapy for head and neck cancer is more contradictory due to the complex anatomy in this region. Specificity ranging from 75% for bone invasion to 90%-95% for muscle invasion has been reported. Specificity is lower for laryngeal and hypopharyngeal tumors (75-85%) and nonspecific nonmalignant changes in signal intensity of the cartilage can account for specificity values as low as 55% [18]. A small study performed by [19] evaluated the effect of including MRI data in patients with advanced head and neck cancer. They noted that tumor extensions seen on CT are not always noticed on MRI and vice versa. Although [20] concluded that CT/MRI fusion improved the determination of target volumes in nasopharyngeal cancer, [21] showed that there was no advan-
mage in using MRI over state-of-the-art CT for the delineation of pharyngo-laryngeal squamous cell carcinoma GTVs, spinal cord, and parotid glands, but hypothesized that MR may be beneficial for patients with nasopharyngeal and ethmoid tumors due to its superior sensitivity for the detection of bone invasion in these sites. Most notably, all the imaging modalities tended to result in overestimation of the tumor extension at the same time as failing to depict a small fraction of the macroscopic tumor extension. Additionally, histological examination often failed to find evidence of infiltration of the thyroid cartilage, despite its being suggested on MR images. In these studies patients were imaged with the body coil in order to use immobilization devices, and so images may not have benefited from an optimal signal-to-noise ratio. [22] demonstrated in a large study that in the identification of both the primary tumor and of the extent of nodal involvement in a group of patients with squamous cell carcinoma of the head and neck, a combination of MR and CT performed less well than PET, although PET cannot provide the detailed information necessary for treatment planning. It would appear from these results that relying solely on changes observed in morphology alone is not sufficient for the accurate identification of cancer. Magnetic Resonance imaging techniques that infer information regarding the tissue function, as well as its form, need to be piloted within the clinical environment and their efficacy assessed.

**Prostate Cancer**

For prostate cancer, MRI can provide better internal organ assessment than CT for disease extent, capsular and seminal vesicle involvement. The superior soft tissue contrast of MRI has previously been shown to demonstrate improved definition of pelvic treatment volumes [23] and a smaller prostate volume than that defined using CT. More recent work [24] found that the volume of the prostate did not differ significantly but that less intra-observer variability was observed with MR. Improved CT-image interpretation and the ability to use reconstructed CT images in the sagittal and coronal planes may lead to greater similarity in the definition of prostate volume. However, a continuing advantage of MR over CT is its potential to identify dominant intra-prostatic lesions. As local failure after radiotherapy for prostate cancer predominantly occurs at the original tumor site, control may be improved by increasing the dose to the original tumor site. The use of $T_2$-weighted MR images employing an endorectal coil for optimal signal-to-noise ratio can produce a diagnostic accuracy of 61% to 88% [25], but can displace and deform the shape of the prostate and surrounding area making such images unsuitable for direct inclusion in radiotherapy planning. The image fusion tools implemented in most commercial treatment planning systems are based on solid-body translations and rotations of the images, and so are unsuitable for this problem. [26] used a narrow band deformable registration model to map prostate images acquired using an endorectal coil onto treatment planning CT images.

Although the sensitivity of $T_2$-weighted images for tumor detection in the peripheral zone is high, specificity is poor and the 30% of tumors that occur in the central gland cannot be detected on $T_2$-weighted imaging [27]. To address this shortcoming more advanced MR imaging methods (such as diffusion-weighted or dynamic contrast enhanced MRI) are being investigated as potential tools [28]. These are believed to reflect, respectively, the increased cellularity and alterations in vascularity associated with the presence of a tumor.

The identification of lymph node involvement is important in the treatment of prostate cancer and recent advances in radiation therapy allow pelvic lymph node irradiation without greatly increasing the dose to critical structures. Neither CT nor MRI, relying predominantly on size criteria, are optimal for the detection of metastatic disease within the lymph nodes. The development of MR contrast agents containing super-paramagnetic nanoparticles that are taken up by healthy rather than metastatic lymph nodes has the potential to improve the accuracy with which MR can identify affected lymph nodes. Although the three examples mentioned above are intended to illustrate some of the more widely used or researched uses in MRI in radiotherapy planning, they are not exhaustive, and there is significant interest in using MRI for the determination of motion-based margins and the assessment of anatomical and physiological change during treatment.

**MAGNETIC RESONANCE SPECTROSCOPY AND RADIOTHERAPY**

Magnetic resonance spectroscopy is used in a wide range of disciplines including physics, chemistry, and biology. In the biomedical context it is used for measuring compounds within fluids, tissue samples, and in vivo. It uses the same general principles and equipment as its widely-used partner, MRI. However, while MRI builds images using signals from $^1H$ nuclei in tissue water (and sometimes lipid) present at concentrations of ~35 M, MRS is used to measure signals from magnetic nuclei in tissue metabolites, such as choline, creatine, and lactate, which are present at much lower concentrations (typically in the order of a few mM). Because most diseases cause a change in the balance of metabolites within affected tissues, MRS may therefore be used to evaluate disease and response to treatment. In particular it can be used for differential diagnosis, both between tumors and benign pathology [29], and between different tumor types [30]. Because MR spectra are acquired using MRI scanners, they are automatically co-registered with MR images, which may then themselves be co-registered with planning CT scans in the normal way, if required. Magnetic resonance spectroscopy does not involve ionizing radiation, and therefore is a relatively safe technique to use. Example spectra from brain and prostate are shown in Fig. (3) to illustrate the type of data that are obtained. Further details of specific metabolites detected in brain and prostate are listed in Table 2 and discussed below. More detailed introductions to the use of in vivo MRS in general [31] and to applications to radiotherapy in particular [32] can be found in the literature.

**Use of Magnetic Resonance Spectroscopy for Radiotherapy Planning**

In the context of radiotherapy, MRS has several potential applications. These include: (1) Identifying tumor extent and metabolically active regions to aid targeting of radiotherapy, (2) evaluating response to treatment, and (3) identifying recurrence.
With the advent of new conformal techniques for radiotherapy, target definition has become one of the main issues in further improving the effectiveness of radiotherapy. In particular, it is necessary to accurately delineate the extent of tumor tissue, and one may also wish to identify regions of high clonogenic cell density which could be targeted with boost doses of radiotherapy using either intensity-modulated external beam radiotherapy or brachytherapy. Conventional imaging methods are often limited in this respect. For example, in the prostate, MRI has better soft tissue contrast than CT [33], but still only has a positive predictive value of 50% . In addition, owing to the different sources of contrast in the two cases the boundaries shown are often different [34]. Because MRS measures tissue biochemistry it has the potential to identify abnormalities and the nature of the abnormality more selectively than morphological imaging can achieve.

Fig. (3a). Example MR spectrum from a single (15 mm)³ voxel in normal brain, illustrating how the required voxel location is selected using MR images. Peaks include creatine (Cr) at 3.9 and 3.0 ppm, Inositol (Ins) at 3.56 ppm, choline compounds (Cho) at 3.2 ppm, N-acetyl aspartate (NAA) at 2.67 and 2.01 ppm, and glutamate glutamine (Glx) at 2.1 – 2.3 ppm. Fig. (3b). Example MRSI data from a patient with prostate cancer. Top left: Transverse image through prostate on which the MRSI is planned. The region edged in green shows the selected region (“PRESS” voxel) within which data are acquired. Top Centre and Right: Transverse MR image with overlying citrate and choline maps based on the MRSI data. Below: Matrix of voxels from Press box. The voxel on the lower left shows high choline and low citrate, typical of cancer, while the voxels on the lower right contain much higher citrate, characteristic of normal prostate metabolism.

Table 2. Details of Some Metabolites Seen in ¹H Spectra of Tissues

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Chemical Shift of Main Peak (ppm)</th>
<th>Number of Equivalent ¹H Nuclei</th>
<th>Multiplicity</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cho</td>
<td>3.2</td>
<td>9</td>
<td>singlet</td>
<td>“Cho” includes contributions from choline, phosphocholine, glycerophosphocholine and other trimethylamines. These metabolites are involved in cell membrane lipid synthesis and breakdown, and are also affected by signaling pathways that can be up-regulated in tumors. Since 9 magnetically-equivalent protons contribute to this peak, relatively low concentrations produce a measurable signal.</td>
</tr>
<tr>
<td>Cr</td>
<td>3.02, 3.9</td>
<td>3, 2</td>
<td>singlets</td>
<td>“Cr” includes creatine and phosphocreatine, which are both involved in energy metabolism.</td>
</tr>
<tr>
<td>Lactate</td>
<td>1.33</td>
<td>2</td>
<td>doublet</td>
<td>Lactate is a product of anaerobic glycolysis, a further aspect of energy metabolism, often being found in necrotic areas</td>
</tr>
<tr>
<td>Lipids</td>
<td>1.3, 0.9 etc.</td>
<td>singlet</td>
<td></td>
<td>Often found in necrotic regions</td>
</tr>
<tr>
<td>myo-Inositol (mL)</td>
<td>3.52, 3.6</td>
<td>2, 2</td>
<td>doublet of doublets triplet</td>
<td>This can be detected in brain using shorter TE acquisitions. Understood to be an essential ingredient for cell growth, an osmolite, and a storage form of glucose.</td>
</tr>
<tr>
<td>NAA</td>
<td>2.01</td>
<td>3</td>
<td>singlet</td>
<td>NAA is considered to be a neuronal marker, so only present in brain.</td>
</tr>
<tr>
<td>Citrate</td>
<td>2.6</td>
<td>1</td>
<td>multiplet</td>
<td>This is synthesized and accumulated by normal prostate epithelial tissue</td>
</tr>
</tbody>
</table>
Acquiring Magnetic Resonance Spectra for Radiotherapy Planning

Volumes selected for acquisition of MR spectra are positioned using MR images acquired in the first part of the same examination. The MRS and MRI data are therefore inherently co-registered. However, while MR images have better soft tissue contrast compared with CT images, they suffer distortions and do not intrinsically provide electron density information, as discussed earlier. For regions outside the head, motion during the scan needs to be minimized. For studies of the prostate it is common to use agents such as Buscopan to reduce peristalsis. Data acquisition can be synchronized to the heart or breathing cycle using cardiac or respiratory triggering, while “navigator echoes”, an MR technique that identifies a column of tissue and monitors movement along this column, may also be used. It is not possible to eliminate motion entirely, and as with conventional CT techniques, this must be remembered when prescribing the margins for irradiation. As the application of MRI and MRS for radiotherapy planning develops, it is likely that use of immobilization devices will be evaluated in more detail.

Current Status of Magnetic Resonance Spectroscopy in Radiotherapy Planning

$^1$H MRS packages are currently available for most commercial clinical MR scanners, usually including both single-voxel localization techniques and magnetic resonance spectroscopic imaging (MRSI). However, owing to the extra expense and the time required to perform MRS examinations, many hospitals choose not to have this option. The packages are increasingly easy to use, but previous experience is important to achieve good results and to understand the reasons for technical failures. Assuming that diagnostic MR images have already been acquired, the extra time required for $^1$H MRS is typically a few minutes for single-voxel techniques, and 10-15 min for MRSI, yielding a total exam time of typically 45 - 60 min. Some software for spectral processing is usually provided, but for quantitative work many users choose to export their data to specialist spectral processing software. Magnetic resonance spectroscopy using nuclei other than $^1$H is less common owing to the requirement for additional hardware. Scan times are also usually longer.

While MRS has great potential to aid target identification in radiotherapy planning, it has only been used for this purpose in a few specialist research centers, primarily in brain and prostate studies. This is because MRS has only recently become available in a form that is relatively easy to use, it requires extra time for data acquisition, and few clinical studies have yet been done to demonstrate an advantage in use. Owing to signal-to-noise ratio limitations, the best spatial resolution achievable (~ 6-10 mm) is larger than one would like. While it is intuitive that better targeting of treatment should lead to improved response, large trials are required to demonstrate in practice that MRS data would help. This is likely to happen in two steps: firstly to investigate correlations between MRS observations and survival or local recurrence based on existing treatments, and then to demonstrate improvement in survival when MRS data are included in the definition of target volume.

Target Identification and Differential Diagnosis

In the brain (Fig. (3a)), MR spectra include contributions from total creatine (Cr) (3.94 and 3.01 ppm), total choline (Cho) (3.22 ppm), N-acetyl aspartate (NAA) (2.01 ppm), myo-inositol (ml) and glycine (3.55 ppm), lactate (Lac) (1.35 ppm), alanine (Ala) (1.47 ppm), contributions from a range of lipid resonances (lip) (0.9, 1.3 ppm), broad resonances due to macromolecules (2.05-2.8, 5.4 ppm) and poorly resolved amino acids such as glutamate and glutamine (Glx) (~ 2.3 ppm). MR spectra of astrocytomas show elevated Cho, reduced Cre and significantly reduced NAA [35]. In the brain MRS can be used both to aid differential diagnosis of brain tumors, and in identifying tumor extent. The metabolic abnormality does not always match that seen using contrast-enhanced MRI [36]. A study of survival following gamma knife surgery [37] showed that patients with poor overlap (< 50%) between treatment volume (based on conventional imaging methods) and volume of metabolic abnormality had reduced survival compared with those having good overlap, suggesting that the MRS-defined lesion was important.

The main spectral peaks observed in normal prostate (Fig. (3b)) are those of the choline-containing compounds (Cho) at 3.2 ppm, creatine and phosphocreatine (3.02 ppm) and a large peak from citrate (2.6 ppm). In prostate cancer choline is elevated and the normal production of citrate is reduced. In contrast, benign prostatic hyperplasia, an enlargement of the prostate commonly found in older men, is characterized by high levels of citrate. Hence the choline/citrate ratio is a fairly reliable measure of the presence of cancer. MRSI has been used in combination with MRI to define regions for dose escalation within the prostate [38], permitting a dose of > 90 Gy to the high-risk region while treating the remainder of the prostate to ~ 70 Gy.

$^1$H MRSI data may be acquired from the prostate using an external phased-array coil. However the best signal-to-noise ratio is achieved using an internal endorectal coil. This is usually well tolerated by patients. The main disadvantage of the endorectal approach is slight deformation of the prostate which needs to be allowed for when using the images for radiotherapy planning. One study suggests that rigid endorectal coils are less of a problem in this respect than the more usual balloon coils [39]. Buscopan is often used to reduce involuntary motion. Currently the state-of-the-art at 1.5 T is to achieve voxels with a 3D isotropic resolution of 6.25 mm in an acquisition time of 17 minutes [40]. Studies have shown that owing to hemorrhage there is some degradation of in vivo spectra in the eight weeks following trans-rectal biopsy (18.5% of peripheral zone voxels have been reported as degraded within 8 weeks of biopsy, and 7% for those examined more than 8 weeks after biopsy [41]).

Validation

Owing to the difficulty of obtaining biopsy samples from brain, more validation studies have been done in prostate. A strong correlation has been found between negative MRSI and negative biopsy findings, and between positive MRSI and positive biopsy findings [42]. However, there is only a weak correlation between the concentration of prostate specific antigen (PSA, the current “gold standard”) and either
biopsy or MRSI findings. Step-section pathologic examination of radical prostatectomy specimens demonstrated that MRI combined with MRS yielded a significant improvement in cancer localization to a prostate sextant (left or right; base, mid-gland or apex) compared with MRI alone [43]. Several studies have shown that adding MRSI to an MRI exam increases the accuracy of diagnosis. One particular area of high current interest is in discriminating the many patients who present with elevated PSA but who have pathologically indolent cancer from those with aggressive disease; preliminary studies suggest that MRSI also has a useful role to play here [40]. High-resolution studies of tissue biopsy samples support these findings, with linear correlations measured between metabolite levels characteristic of normal epithelium or of prostate cancer, and the proportions of the corresponding cells as measured by computer-aided image analysis of prostate pathology slides [44].

Recurrence

Magnetic resonance spectroscopy has been shown to help identify patients at risk of recurrence. [45] have indicated elevated Lip/Cr and Lac/Cr in the peri-tumoral region of high grade glioma. It has also been suggested that areas of relatively high Cho/NAA may indicate high cellular activity, and hence radio-sensitivity, and Lac may indicate hypoxic areas with reduced radio-sensitivity. The technique can also be helpful in identifying areas missed by radiation fields, and in separating recurrence from radiation necrosis. Adding MRSI to MRI has been shown to substantially improve the identification of tumor recurrence following external beam radiotherapy (the area under the ROC curve, a measure of the effectiveness of a test, increased from 0.5 to 0.81 [46]).

Treatment Response

Magnetic resonance spectroscopy may also be used to monitor response to treatment. For example, reduction in Cho [47] and in lipid and lactate [48] can reflect response to chemotherapy and radiotherapy. Reductions in Cho and Lac and an increase in Lip (believed to represent necrosis) in responding tumors were detected at an earlier time (1 week to 1 month) than contrast-enhanced MRI or 201TlCl [49].

Relative Merits and challenges of Magnetic Resonance Spectroscopy in Radiotherapy

Magnetic Resonance Imaging already plays a major role in identifying the extent and position of tumors, aiding delineation of target volumes. Magnetic resonance spectroscopy provides the ability to observe aspects of tissue metabolism, which is a more direct reflection of tumor activity and of therapeutic response. The ability to obtain this information during the same examination as the anatomical and functional MRI images is a major advantage compared with other techniques. While the number of studies so far is limited, there is strong evidence that MRS may have a valuable role in radiotherapy planning. The main limitation with MRS is that voxel sizes of at least (6 mm)3 to (10 mm)3 are required to achieve an adequate signal-to-noise ratio. Thus, small infiltrating lesions are unlikely to be detectable. It also needs to be remembered that the edges of target volumes defined from spectroscopic images for treatment planning, although smoothed and interpolated for presentation, in fact are limited by this same spatial resolution and will also include some blurring from point spread function effects. While some improvement in sensitivity and spectral specificity is expected with higher field scanners and improved sensitivity coils, this is likely to yield only a small improvement in spatial resolution. On the other hand, it is increasingly clear that while in principle both MRI and CT have much better spatial resolution, MRS has the potential to improve identification of the gross tumor volume and hence improve treatment using radiotherapy.

ACKNOWLEDGEMENTS

The authors wish to thank Drs Kate Newbold and Mike Partridge for their comments on the manuscript.

REFERENCES


