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Dynamic contrast-enhanced MR imaging

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Introduction

MR imaging has been proposed and tested, both experimentally and clinically, as a method to characterize tumours with respect to their state of angiogenesis. The available approaches can be divided into intrinsic (non-enhanced) and contrast media-enhanced methods; the latter can be further divided by the type of contrast medium, small molecular agents that distribute rapidly in the extracellular space (so-called non-specific or ECF agents), large molecular agents designed for prolonged intravascular retention (so-called macromolecular contrast media, MMCM, or blood pool agents) and targeted agents intended to accumulate at sites of concentrated angiogenesis mediator molecules. ECF contrast agents are available commercially and are the focus of this review. Macromolecular contrast media are themselves undergoing clinical trials, but are not currently approved for human use. Molecular targeted contrast media are in preclinical development.

Contrast agent dynamics using extracellular contrast agents

Clinical dynamic contrast-enhanced MRI (DCE-MRI) studies are able to distinguish benign from malignant tissues by exploiting differences in contrast agent kinetics to extracellular contrast agents. These agents are freely diffusable, and readily pass from the vasculature into the extravascular–extracellular space and therein give rise to parenchymal enhancement. Numerous studies have shown that malignant tumours frequently reveal faster and higher levels of enhancement than normal surrounding tissues[1–4]. These differences occur because DCE-MRI is sensitive to abnormalities of tumour microcirculation. These are the networks of vessels with diameters of less than 100 (m, which are beyond the resolution of conventional imaging. Tumour microcirculation differs from normal tissues in a number of fundamental ways. These include an increased density of chaotic vessels leading to microcirculatory abnormalities in blood flow (both spatially and temporally). Tumour microvasculature is also hyperpermeable (in most tumours) to low molecular weight compounds including extracellular MR contrast agents. Lastly, the interstitial space of tumours is increased[4,5]. As a result, there are major alterations in all major tissue compartments (vascular, cellular and extravascular–extracellular).

The introduction of fast imaging routines and the development and application of tracer kinetic modelling techniques now allows a fuller understanding of the physiological basis of observations noted in DCE-MR examinations. With optimal data collection, sequences can be designed to be sensitive to tissue perfusion and blood volume (so-called T2* methods) and/or permeability and extracellular leakage space (so-called T1 methods)[6]. These two methods are compared in the Table 1. Such techniques permit the functional aspects of tumour neovascularity to be assessed in vivo in a non-invasive and repeatable way. Other advantages of MRI methods include good spatial resolution and the ability to incorporate physiological data acquisition into routine patient studies.

T2*-weighted imaging

Perfusion-weighted images can be obtained with 'bolus-tracking techniques' that analyse the passage of contrast material through a capillary bed[7]. When a bolus of paramagnetic contrast agent passes through a capillary bed it produces magnetic field (Bo) inhomogeneities that result in a decrease in the signal intensity of surrounding tissues. This effect can be observed with susceptibility-weighted T1- or T2*-weighted sequences, the latter providing greater sensitivity and contrast to perfusion effects. The degree of signal loss seen is dependent on the vascular concentration of the contrast agent and microvessel size and volume.

Tracer kinetic principles can be used to provide estimates of perfusion characteristics, e.g. relative blood volume (rBV), relative blood flow (rBF) and mean transit time (MTT) from the first pass of a bolus

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Table 1 Comparison of T2- and T1-weighted dynamic contrast-enhanced MR imaging techniques*

	T2*W imaging	T1W imaging
MR tissue effect	Darkening	Enhancement
Duration of effect and requirements for measurements	Seconds/subsecond	Minutes/2–25 s
Magnitude of effect	Small	Greater
Optimal contrast dose	0.2 mmol/kg	0.1–0.2 mmol/kg
Quantification method used	Relative more than absolute	Relative and absolute
Physiological property measured	Perfusion/blood volume	Blood vessel permeability, capillary surface area, leakage space
Pathological correlates	Tumour grade and vessel density	Microvessel density Vascular endothelial growth factor
Clinical MR applications	Lesion characterization — breast and brain Non-invasive tumour grading Directing brain tumour biopsy Determining brain tumour prognosis Monitoring treatment e.g. radiotherapy	Lesion detection Improving tumour stage Lesion characterization Predicting response to treatment Monitoring treatment Novel therapies (e.g. antiangiogenesis drugs) Detecting relapse

contrast agent through the microcirculation[8]. These parameters are qualitative or 'relative' because the arterial input function is not typically measured. Recently, quantification of these parameters has been undertaken by simultaneous monitoring of the concentration of contrast agent in large neck or brain vessels[9]. MRI systems capable of rapid image acquisition are required to characterize these effects adequately. High specification, echo-planar capable systems are suited to this task allowing rapid, multi-slice acquisition. However, such studies are possible on conventional MRI systems using standard gradient-echo techniques but are limited to a few slices. The quantification techniques described above also cannot readily be applied to areas of marked BBB breakdown or to extracranial tumours with very leaky blood vessels. This is because the T1-enhancing effects of gadolinium chelates predominate and counter the T2* signal lowering effects, resulting in falsely low blood volume values. Currently, solutions for obtaining more reliable perfusion data under these circumstances are being investigated. These include optimization of pulse sequence parameters to minimize T1 effects[10] and techniques that aim to take into account the relative contribution of T1 and T2* components in DCE-MRI studies. Another approach is to use non-gadolinium-based susceptibility contrast agents based on dysprosium, which has a strong T2* effect but a weak T1 effect[11].

The signal loss observed with T2*-weighted sequences has been used qualitatively in clinical studies to characterize liver, breast and brain tumours. Ichikawa *et al.* were successfully able to discriminate between liver metastases, haemangiomata and hepatocellular carcinoma on the basis of characteristic morphological signal intensity changes on echo-planar imaging[12]. The explanation for their observations depends on pooling of contrast medium, which results in signal loss that is greater for lesions with large vascular pools (e.g. haemangiomata and hepatomas). Perfusion imaging can also characterize breast lesions[13,14]. These studies showed strong decreases in signal intensity in malignant tissues, whereas susceptibility effects in fibroadenomas were minor. The pathophysiological explanation for this observation probably relates to differences in microvessel arrangements, density and size in malignant tumours and fibroadenomas[15].

Quantitative imaging is currently restricted to normal brain and brain lesions with an intact blood brain barrier (BBB) because the contrast agent is retained within the intravascular space. Relative cerebral blood volume (rCBV) mapping can be used to detect areas of increased vascularity in brain gliomas[16,17]. Areas of high tumour rCBV appear to correlate with higher degrees of mitotic activity (information on tumour grade) and vascularity but not with cellular atypia, endothelial proliferation, necrosis or cellularity[16]. In non-gadolinium-enhancing gliomas (that is, those with an intact BBB), homogeneous low rCBV is found in the lowest grades, whereas higher grade tumours display both low and high rCBV components. Relative CBV maps appear to have a high negative predictive value in excluding the presence of high grade tumour in untreated patients regardless of their enhancement characteristics on T1-weighted MRI. Cerebral blood volume maps can therefore be used to direct stereotactic biopsy to areas of highest grade[18,19,44]. Other potential uses of perfusion imaging in patients with brain tumours could include distinguishing radiation necrosis from recurrent disease, determining prognosis and monitoring response to treatment[20].

T1-weighted imaging

Gadolinium chelates readily pass from the blood into the extracellular space of tissues at a rate determined by the permeability of the capillaries and their surface area. The early phase of contrast enhancement (often referred

to as the 'first pass') includes the arrival of contrast medium and lasts many cardiac cycles. In this phase, the contrast medium gains access to the extracellular space via diffusion and causes shortening of tissue T1-relaxation times. The contrast medium also begins to diffuse into those compartments further removed from the vasculature including areas of necrosis and fibrosis. Later (minutes), the contrast agent diffuses back into the vasculature from which it is excreted (usually by the kidneys). During this late phase, contrast medium elimination from slow-exchange tissues also occurs explaining the 'target like' enhancement characteristic of some tumours.

Most studies have attempted to correlate tissue MR enhancement with immuno-histochemical microvessel density (MVD) measurements. Some studies have shown positive correlation between tumour enhancement and MVD[21–25], whereas others have found no correlation[26,27]. Thus, the microvascular volume, directly related to the MVD, cannot be assumed the only or primary determinant of tumour enhancement; the rate of diffusion of contrast agent into the interstitial space is also considered critical. Recently, vascular endothelial growth factor (VEGF) distribution a known, potent vascular permeability and angiogenic factor, has been implicated strongly as an additional explanatory factor that determines MR enhancement. Knopp *et al.*[28] recently reported that vascular permeability (measured as the constant K_{21}) closely correlates with tissue VEGF expression in breast tumours. The probable role of VEGF in determining microvascular permeability is supported by the spatial association of hyperpermeable capillaries and VEGF expression shown on correlative MR-histological studies[29]. Furthermore, the observation that MR permeability measurements can detect suppression of vascular permeability after anti-VEGF antibody[30] and after the administration of inhibitors of VEGF signalling[31] lends weight to the important role played by VEGF in MR permeability.

The degree of signal enhancement seen on T1-weighted images is dependent on a number of factors including tissue perfusion, capillary permeability to contrast agent, volume of the extracellular leakage space, native T1-relaxation time of the tissue, contrast agent dose, imaging sequence and imaging parameters, also on machine scaling factors[32]. Objective analysis of T1-weighted contrast-enhanced MR images can be performed: (1) by measuring signal intensity changes (semi-quantitative analysis); and/or (2) by fitting pharmacokinetic models to the tissue contrast medium concentration–time curves (quantitative analysis).

Semi-quantitative descriptors of contrast enhancement include onset time, initial and mean gradient of the upsweep of enhancement curves, maximum signal intensity and washout gradient. As the rate of enhancement may improve the specificity, an additional time element can also be used, e.g. maximum intensity time ratio (MITR)[33] and maximum focal enhancement 1 min after contrast medium administration[34]. Others have categorized time–signal intensity curve shapes and correlated them with breast lesion types[28]. Semi-quantitative parameters have the advantage of being relatively straightforward to calculate but have a number of limitations including the fact that they do not accurately reflect contrast medium concentration, are dependent on the imaging sequence and image acquisition parameters, and are not physiologically based. These limitations can hamper comparisons between and within patients and between different imaging centres.

Quantitative analysis of dynamic contrast-enhanced MR images using pharmacokinetic models can provide estimates of physiological parameters such as the transfer constant K^{trans} (formally called permeability-surface area product per unit volume of tissue), the volume of extravascular extracellular space (EES) per unit volume of tissue (V_e) and the rate constant (k_{ep} also called K_{21}). These standard parameters have recently been reconciled with others that appear in the literature[35]. If the contrast agent concentration can be measured accurately and the type, volume and method of administration are consistent, then it may be possible to directly compare pharmacokinetic parameters acquired serially in patients and between patients imaged at different scanning sites. Quantitative parameters are more complicated to determine than those obtained using semi-quantitative methods. The model chosen may not fit the data obtained, and each model makes a number of assumptions that may not apply to every tissue or tumour type[35,36].

Analysis of dynamic T1-weighted images is a valuable diagnostic tool in a number of clinical situations. Its role in detecting sub-clinical disease remains to be determined and may include screening of subjects at high genetic risk of breast cancer; the latter application of DCE-MRI is the subject of several ongoing clinical trials. A more established role is in lesion characterization where it has found a role in distinguishing benign from malignant breast and musculoskeletal lesions[3,28]. Simple observations from time–signal–intensity curves have shown that malignant tissues generally enhance early, with a rapid and large increase in signal intensity

Figure 1 **Benign vs malignant lesions (morphology, enhancement patterns and permeability maps). Top row: morphological images; middle row: time–relative signal intensity curves from regions illustrated on morphological images; transfer constant maps (K^{trans}), colour scale 0–2 min. In general, benign lesions even when large, remain homogeneous morphologically and in their enhancement characteristics (on both regions of interest and parametric analysis) compared with malignant lesions that often enhance heterogeneously. This figure is reproduced from 'Breast MRI in Practice' Editors: Ruth Warren and Alan Coultard, Harwood Academic Publishers, copyright Overseas Publishers Association N.V. with permission from Gordon and Breach Publishers.**

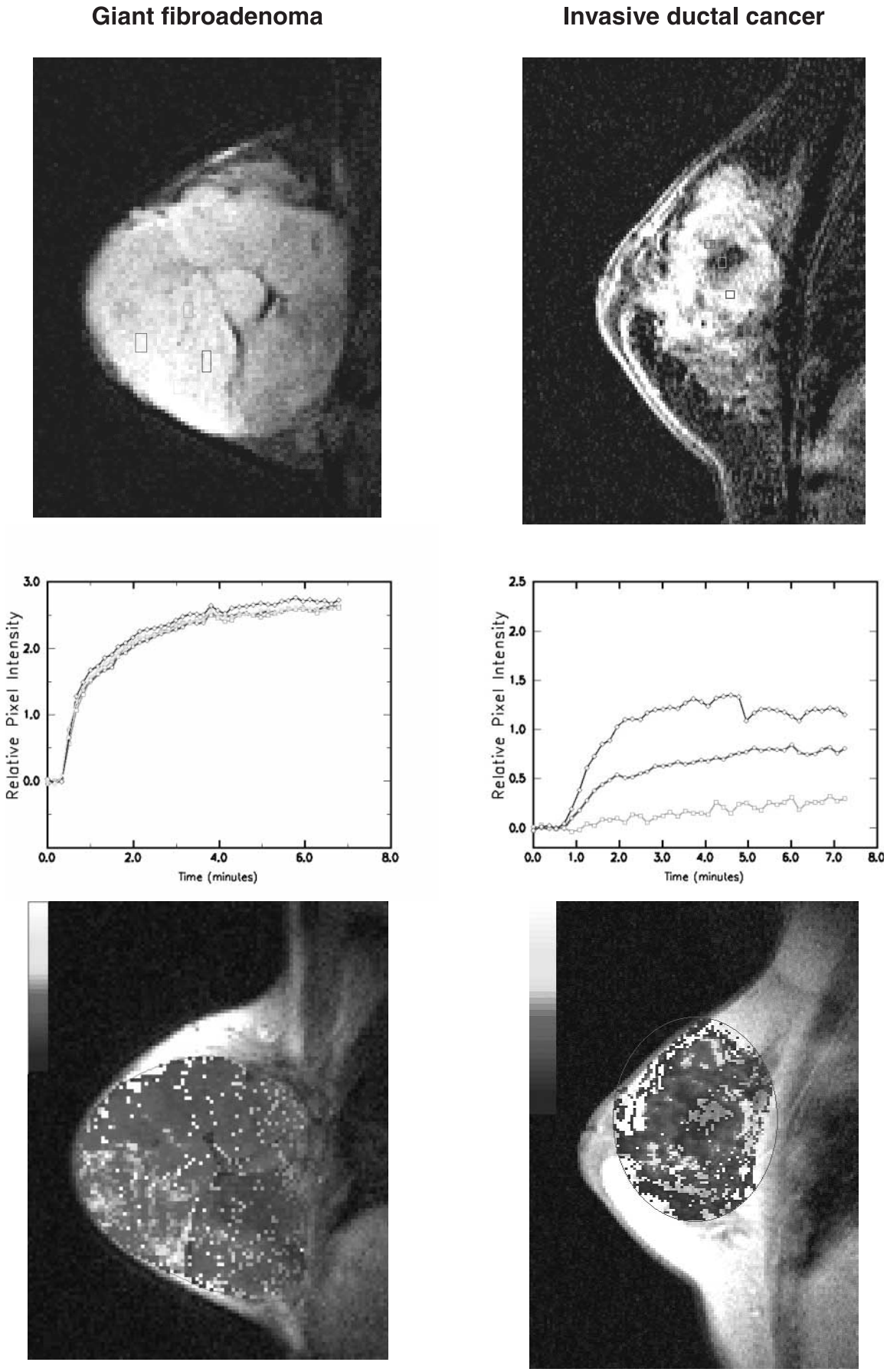
Giant fibroadenoma
Invasive ductal cancer
Relative Pixel Intensity
Time (minutes)
Relative Pixel Intensity
Time (minutes)

Figure 1.

compared with benign tissues, which in general show a slower increase in signal intensity. In the breast, sensitivities for this discrimination have been high but specificities have been more variable, with fibroadenomas sometimes demonstrating an enhancement pattern similar to that of invasive cancer. Dynamic T1-weighted MRI studies have also been found to be of value in staging bladder and prostate cancer[2,37]. Dynamic MRI is also able to predict or monitor the effects of treatment in patients with osteosarcomas and in breast, prostate and cervix cancers[38–41]. Quantitative changes in contrast enhancement have been observed prior to changes in tumour volume. It is not currently clear whether such changes occur before changes in metabolism that may be detectable by positron emission tomography (PET) or MR spectroscopy. Most recently, Hawighorst *et al.* have shown that enhancement parameters can predict patient survival in cervical cancer[23]. More specifically, patients with tumours that had a fast initial rate of enhancement high or permeability were more likely to have a poorer prognosis[23]. Contrast-enhanced T1-weighted studies have also been found to be of value in detecting relapse within treated tissues.

Presentation of dynamic MR data and dealing with heterogeneity (Fig. 1)

Most current dynamic MRI studies apply user-defined regions of interest (ROI). ROI methods yield enhancement curves with good signal-to-noise ratio, but lack spatial resolution, are prone to partial volume averaging errors and ignore the heterogeneity of tumour enhancement. The placement of ROI can have a profound effect on the outcome of the analysis. In its simplest form, ROI encompassing the whole tumour can be drawn from which an average enhancement curve is extracted. This method is acknowledged to be inappropriate because many malignant tumours show markedly heterogeneous areas of enhancement. This regional variability of enhancement probably reflects variations in microvessel density (microvessel 'hot-spots' referred to above), VEGF, areas of fibrosis, avascularity and necrosis. Therefore, selective sampling of regions within a tumour is used by most researchers, based on the premise that the discrimination of lesions is improved by using selective sampling of enhancement characteristics[42].

Another approach of displaying dynamic data is by the use of pixel mapping. In this technique, quantitative enhancement information is displayed as a colour map exactly co-registered with the anatomic images on a pixel-by-pixel basis. This type of display has a number of advantages including an appreciation of heterogeneity of tissue enhancement and removal of the need for selective placement of user-defined ROIs. The risk of missing important diagnostic information and of creating ROIs that contain more than one tissue type is thus reduced. Pixel mapping techniques also enable improved visualization of changes in tumour microvascular function in response to treatment. Recently, histogram analysis has also been used to quantify the heterogeneity of tumours for comparative and longitudinal studies and thus allow a method for monitoring the effects of treatment and can also show the regression or development of angiogenic hotspots. Pixel mapping techniques have the disadvantages of having poorer signal-to-noise ratio and requiring specialist software for their generation[43].

Future trends

Technical developments in MRI hardware and software are likely to continue so enabling more rapid, high spatial resolution, multi-slice and simultaneous T1 and T2* image acquisitions. Current techniques are limited to body parts with little physiological movements, but motion compensation techniques based on navigator technologies may overcome these restrictions. The accuracy of perfusion and permeability measurements is dependent on the compactness of the bolus injection of the contrast medium and in this regard, the recent availability of MR-compatible automated injection devices is welcome. Non-gadolinium and intravascular contrast agents with different pharmacokinetic properties will potentially extend the clinical usefulness of such measurements. Intravascular contrast agents with dominant T1 or T2* properties are currently being developed for human use. These include macromolecular contrast agents that have low permeability through normal vascular endothelium and a body distribution equal to that of blood volume. Refinements in pharmacokinetic modelling analyses will allow an understanding of the physiological basis of contrast enhancement and such techniques are likely to be incorporated into imaging assessments of cancer patients. The validity and accuracy of these techniques should also be assessed and their relative merits compared to complementary methods, e.g. perfusion images obtained by 'spin-labelling' MRI techniques and PET.

In cancer patients, dynamic contrast-enhanced MRI studies are used for lesion detection and characterization, to detect early relapse within treated tissues, to predict the success of therapy and to monitor the effects of treatments. It is in the latter regard that MRI with its inherent quantitative potential is likely to play an increasing part in monitoring the effectiveness of anti-angiogenic drugs. Such treatments may be directed at already formed vessels or against the angiogenic process itself. Contrast-enhanced MRI techniques are ideally suited to monitor the effectiveness of such treatments in vivo. Dynamic contrast-enhanced MRI may ultimately allow the possibility of an individualized approach to cancer management.

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Positron emission tomography in oncology

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Summary

In recent years PET has progressed from being primarily a research tool to being a clinical imaging technique which adds to and complements existing anatomical and functional modalities. A number of clinical applications have been validated and proven cost-effective, the greatest growth in this promising technique being in the field of clinical oncology.

Introduction

The best evaluated and most clinically important tumours in which PET has a clinical role include non-small cell lung cancers, lymphoma, colorectal cancer, brain tumours, head and neck tumours and melanoma. A clinical role is also likely to exist in other tumours, e.g. other gastrointestinal malignancies, breast cancer, germ cell tumours and thyroid cancers but needs to be more fully evaluated. Although clinical PET is still in its infancy a number of studies are emerging which have confirmed that its high sensitivity and specificity make it a cost-effective investigation[1,2].

What is PET?

PET is a nuclear medicine technique which, following the injection of a positron emitting radiopharmaceutical, results in functional, tomographic images. Positron-emitting radionuclides are radioactive elements which emit two 511KeV gamma rays at 180° to one another and are detected in scintillation crystals surrounding the subject. The detector electronics are linked so that two detection events occurring within a certain time window may be called coincident and thus be determined to have come from the same annihilation. Non-coincident events may be rejected, thereby increasing spatial resolution and decreasing scatter. Images may then be reconstructed using standard tomographic techniques.

The advantages of other nuclear medicine techniques over anatomical imaging, including a high sensitivity due to the ability to map functional/metabolic changes before alteration in structure, are shared by PET. Some of the disadvantages of conventional nuclear medicine imaging are overcome. In addition to having a higher spatial resolution, PET is able to take advantage of some of the biologically important elements which have positron-emitting isotopes such as carbon, nitrogen and oxygen. This means that many organic compounds can be labelled by substitution with a radionuclide without disturbance of normal biochemical pathways. However, PET tracers tend to have short half-lives compared with radiopharmaceuticals used in other nuclear medicine imaging. Because of improved quantitation and the ability to correct accurately for photon attenuation, it is possible to measure uptake of radiopharmaceuticals or dynamic physiological processes in absolute units, e.g. regional cerebral metabolic rate of glucose (rCMRGlc) in mmol/min/g.

One of the perceived disadvantages of PET is related to cost. An on-site cyclotron is required for some of the shorter lived radionuclides although the most commonly used radiopharmaceutical, 2-^{18}fluoro-2-deoxy-D-glucose (^{18}FDG), has a half-life of 110 min which allows transport between distant sites and might, in the future, be a way of reducing radiopharmaceutical costs. More recently, gamma cameras have been developed, with

adaptions including thicker collimators or coincidence electronics, as a low-cost alternative for imaging positron emitting radionuclides. Although promising wider availability, this method has not been evaluated fully enough at the present time for it to become accepted as a routine clinical tool.

The role of clinical PET in oncology tends to be quite specific and does not necessarily replace conventional nuclear medicine or anatomical modalities. In contrast, it offers a complementary procedure for supplying functional and metabolic information, often in the light of structural change. The structural/functional relationship can be further enhanced by co-registration of images, where the high resolution of PET allows anatomical landmarks to be more easily identified, allowing functional information to be accurately superimposed on high resolution morphological data from either computed tomography (CT) or magnetic resonance images (MRI).

The most widely used PET radiopharmaceutical is ^{18}FDG which behaves as an analogue of glucose. It has been recognized for many years that most malignant tumours exhibit increased glycolysis compared with other tissues and it is this property that is exploited in oncological ^{18}FDG PET imaging[3]. A number of tumours have been shown to overexpress glucose transporter membrane proteins identifying a mechanism by which uptake of ^{18}FDG may occur[4]. Of course, increased glycolysis is not specific to tumours[5] but in most clinical situations the degree of uptake either qualitatively or quantitatively allows differentiation of malignant from benign tissue.

The most widely used and computationally simple quantitative method is the measurement of the standardized uptake value (SUV) which is the fraction of injected dose accumulated in a given volume of tumour tissue, normalized to body weight and measured at a specific time post injection (usually at 1 h).

Other potential tracers for cancer imaging include ^{11}C-methionine to study tumour amino acid transport and ^{11}C-thymidine and analogues to measure tumour proliferative activity in vivo. The flexibility of PET radiochemistry is also allowing the development of tracers to study tumour hypoxia, multidrug resistance, angiogenesis and apoptosis.

PET in clinical oncology

It should be noted that PET is not uniformly sensitive and specific over the full range of cancers and at the present time its use should be reserved for properly validated and specific clinical indications. Some tumours show little affinity for ^{18}FDG (e.g. neuroendocrine tumours[6]) while some benign conditions may mimic malignant activity[5].

PET is especially effective in the pre-operative staging of those malignant tumours which have a high 'recurrence' rate. The use of PET in the pre-operative staging of lung cancer is particularly valuable. It has been shown that nearly one-third of patients deemed operable by CT criteria had unsuspected lesions identified with PET and 18% had management changed to a non-surgical regime[7].

Although PET would appear to be very sensitive for tumour detection, the lack of definition of neighbouring structures means that in most circumstances a surgeon would also need anatomical cross-sectional imaging before operating. The functional nature of PET may be advantageous in assessing local lymph node status. CT relies on lymph node size as a criteria for detecting tumour involvement but because of its functional nature, ^{18}FDG PET is able to detect either presence of tumour within small lymph nodes or alternatively to be able to differentiate malignant involvement from reactive changes in nodes which are positive by CT criteria.

Another advantage of PET over other imaging modalities in the staging of tumours is that virtually all tissues within the body can be assessed within a single examination with information being available on the primary tumour, local and distal lymph nodes and visceral and skeletal metastases. An example of this is in the initial staging of lymphoma where ^{18}FDG PET has been consistently more sensitive and specific than clinical or anatomical imaging[8]. An area where ^{18}FDG PET has been less effective is in the detection of brain metastases. This may be because of difficulty in identifying foci of uptake on a background of normal high accumulation.

Because of the relative ease of imaging the whole body with PET it is a useful technique in patients in whom there is a high clinical suspicion of cancer (e.g. those presenting with a paraneoplastic syndrome or those in whom recurrence is suspected due to a rise in tumour markers) which remains elusive by conventional imaging techniques. The whole body imaging capability is also advantageous in those patients who present with a histologically confirmed metastasis but in whom the primary tumour is unknown.

A number of situations arise where either a mass is inaccessible to biopsy or the histology is indeterminate and PET may be suitable as an alternative, non-invasive investigation. ^{18}FDG PET has been used successfully to differentiate indeterminate pulmonary nodules in a number of studies, with malignant nodules showing high uptake of tracer. In comparing a strategy which combines PET and CT in the evaluation and management of indeterminate nodules with other strategies that are currently used, e.g. watch and wait, a surgery-based strategy and a strategy based on CT alone, it has been proposed that the inclusion of PET is cost-effective, leading to possible overall savings of $63 million per year in the US[2].

As the degree of tracer accumulation correlates with the grade of malignancy in many tumours, PET may be used to give information on tumour grade or dedifferentiation if further biopsy is to be avoided. The degree of uptake may also be related to prognosis because of this[9]. This is best illustrated in brain tumours where

^{18}FDG PET may detect dedifferentiation of recurrent tumours[10] but may also be helpful in guiding biopsies to the areas of most active metabolism, ensuring representative specimens for histological analysis[11].

A major deficiency in cancer treatment at the present time is the inability to predict, or assess accurately, response to treatment. In consequence, many patients experience the side effects of therapy from which they will not benefit and others may receive unnecessary or inappropriately prolonged treatment. To date there are limited data but PET appears a promising technique to predict clinical outcome at an early stage, perhaps after one or two cycles of chemotherapy.

The ability of PET to map metabolism rather than structure has also led to it being used to help differentiate post-treatment changes from residual tumour in a number of cancers. This may be especially helpful in areas where cross-sectional anatomical imaging is often difficult to interpret, e.g. pelvic recurrence of rectal carcinoma following radiotherapy, mediastinal mass in lymphoma and the differentiation of post-treatment gliosis from recurrent tumour in primary brain neoplasms.

The clinical use of PET is likely to continue to increase in the next few years as further clinical centres are due to open in the UK. Its ability to provide unique information on metabolism and function in well-defined clinical situations is sure to establish it as a valuable technique amongst the other modern imaging modalities available. There is now growing evidence of its advantages with regard to patient benefit and cost effectiveness in a number of cancers.

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MR lymphography using ultrasmall iron oxide particles (USIOP) in nodal staging of bladder and prostate cancer

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Introduction

Detection of lymph node metastases has very important clinical consequences. If metastatic disease is present, usually curative prostatectomy or cystectomy will not be performed. Current imaging techniques can only show nodal size. Scheidler *et al*. have shown, that both CT and two-dimensional (2D) MRI perform better than lymphography, and that there is a trend towards better performance of 2D MRI vs CT[1].

Recently Jager and co-workers showed that with three-dimensional (3D) high resolution MRI, not only nodal size but also nodal shape can be determined. Taking into account the nodal shape (flat-oval or round)

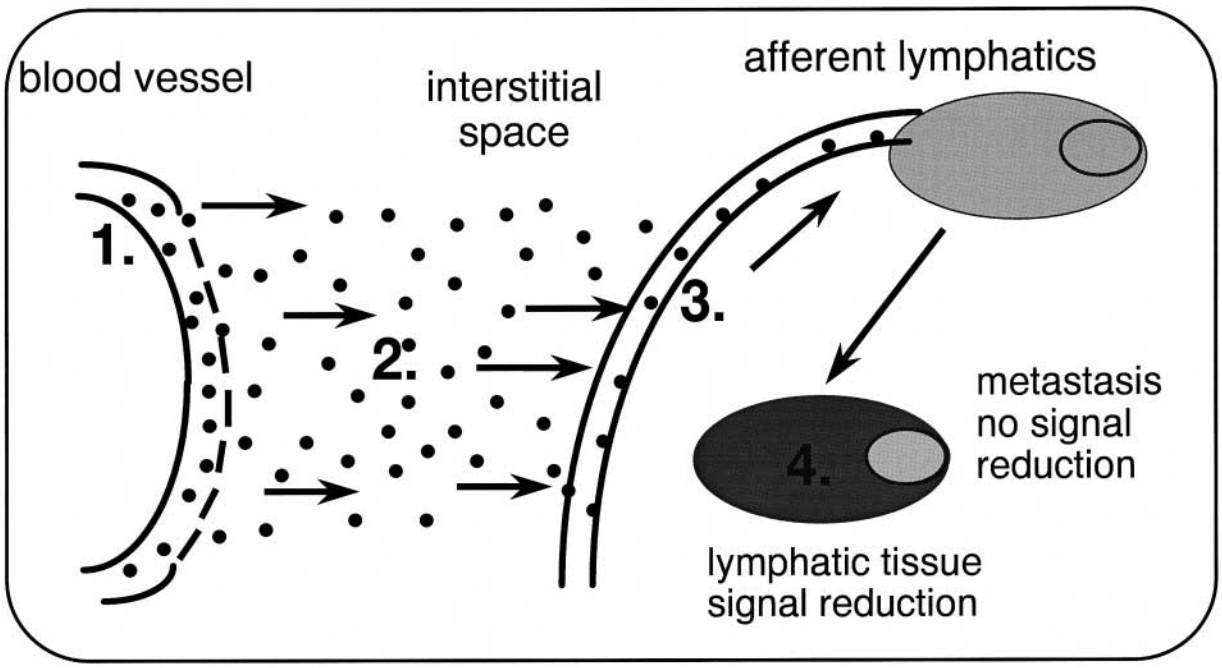

Figure 1 **Uptake scheme of USIOP. (1) Intravenous injection; (2) extravasation to interstitial space; (3) transport through lymph vessels to node; (4) accumulation of USIOP in normal nodal tissue (24–36 h post-injection): normal node will become black (T2*-effect), metastases will have unchanged or higher signal (T1-effect).**

also improved their results. However, in their study, metastases in normal size lymph nodes (<10 mm in flat-oval nodes, <8 mm in round nodes) were still missed, resulting in low sensitivity[2].

On fast dynamic MRI normal size metastatic nodes show early enhancement, however, non-metastatic nodes may also enhance. Therefore, fast dynamic contrast enhanced MRI increases sensitivity, but decreases specificity[3].

Despite the fact that ultrasmall iron oxide particles (USIOP) have been reported to show internal lymph node morphology, metastases in small nodes could not be detected[4]. A possible explanation may be the fact that sequences and contrast dosage were not optimal in this study.

Purpose

The purpose of this study is to increase the sensitivity of MRI in detecting lymph node metastases, that is to recognize metastases in normal size nodes, and at least maintaining high specificity by using an optimal dose of USIOP and high resolution 3D T1-weighted and 2D T2*-weighted sequences.

Materials and method

In a prospective study 59 patients with histologically proven invasive urinary bladder (UBC, $n=29$) or prostate cancer (PC, $n=31$) were examined at 1.5 T (Siemens Vision, Erlangen, Germany) using a body phased-array coil. Before and 24–36 h after intravenous infusion of USIOP (particle size 30 nm; Sinerem, Guerbet, Paris, France) at a dose of 2.6 mg Fe/kg MR images were acquired using high resolution 3D T1-weighted and 2D T2*-weighted sequences. Figure 1 shows how USIOP is transported to the lymph nodes. The T2*-weighted MEDIC sequences were acquired in planes parallel to the iliac vessels ('obturator' planes), the FLASH T2*-weighted sequences in the axial plane. The 3D sequences were evaluated by soft-copy reading using multiple planes.

On the pre-contrast MRI lymph nodes were rated positive based on size and shape criteria described by Jager *et al.*[2] (flat-oval node >10 mm, round node >8 mm). On the post-contrast MRI lymph nodes were rated positive if they showed partial or total missing of signal loss on both sequences, especially on the T2*-weighted sequece. The MR-findings were prospectively evaluated by one experienced observer in each centre (Berlin $n=21$ MT, Nijmegen $n=38$ JOB).

Results of pre- and post-USIOP MRI were compared with histopathology on a patient-by-patient basis. Fifty-seven patients had lymphadenectomy, two had a positive biopsy. Statistical analysis was performed to calculate differences in accuracy, sensitivity, specificity, negative and positive predictive value, using the *t*- or Wilcoxon test depending on the distribution of the variation.

Results

Normal nodal tissue showed signal loss 24–36 h post-injection. Metastases showed an equal or higher signal.

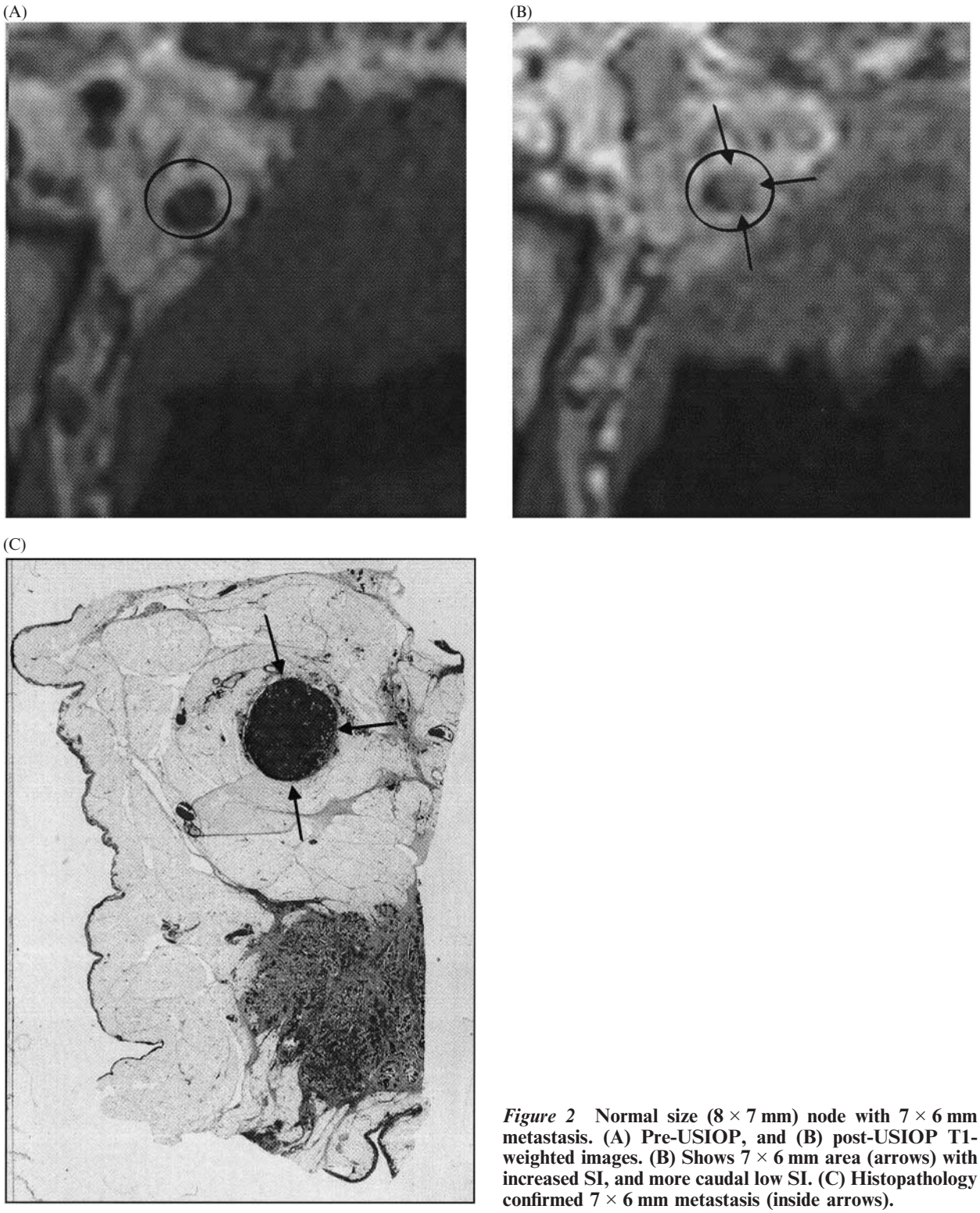

Figure 2 **Normal size (8 × 7 mm) node with 7 × 6 mm metastasis. (A) Pre-USIOP, and (B) post-USIOP T1-weighted images. (B) Shows 7 × 6 mm area (arrows) with increased SI, and more caudal low SI. (C) Histopathology confirmed 7 × 6 mm metastasis (inside arrows).**

On the 3D T1-weighted MP-RAGE sequence vessels, especially veins, showed high signal intensity, thus resulting in better separation from the nodes. On the MEDIC sequence in most patients the vessels showed low SI.

Pre-contrast MRI showed 12 patients to be true positive, 32 to be true negative, 11 to be false negative and 4 to be false positive. With post-USIOP MRI 21 patients had true positive, 33 true negative, 2 false negative and 3 false positive results. Sensitivity and

accuracy and negative predictive value showed a significant improvement using post-USIOP (respectively from 52% to 91%, 75% to 92% and 74% to 94%, $p=0.01$, 0.02 and 0.01). This was due to the detection of metastases in normal size nodes. Eleven of the 23 patients with positive nodes had metastases in normal size nodes (<8 mm). In nine of them these could be detected prospectively on post-USIOP images only. The size of the metastases in these nodes ranged from 7 to 3 mm (Fig. 2). Despite higher sensitivity specificity remained equal from 89% to 91%. In one patient enlarged reactive nodes could be correctly recognized as non-metatstatic by their decreased SI on the post-USIOP images.

In one patient on post-USIOP images extra-nodal disease was prospectively recognized, which was confirmed at surgery.

During the slow (30-min) infusion of the USIOP-contrast only one patient showed minor side effects (low back pain), which was due to a too rapid infusion. After slowing down the infusion rate the symptoms decreased, and no further treatment was needed.

Discussion

On post-USIOP MRI the internal nodal structure can be visualized even in small (<8 mm) nodes. Thus it is possible to separate normal lymphatic tissue from metastases. This results in a significantly better recognition of metastases in normal size nodes: sensitivity improves from 52% to 91%, with equal high specificity.

Possible explanations for these better results compared with earlier studies[4] are:

(1) the combination of the use of a 3D T1-weighted and a high resolution T2*weighted sequence;
(2) a more optimal contrast dose;
(3) the use of the 'obturatur' (=semi-sagittal) planes for evaluation; and
(4) special care in using the MR-findings to locate small metastatic nodes during surgery.

Only thanks to knowing the location of a small metastatic node, as shown by post-USIOP MRI, laparoscopic and laparotomic lymph node dissection were positive in two patients. This may also explain the relatively high number of small metastatic nodes (48%) found in this study.

The findings of post-USIOP MRI have important clinical consequences:

(1) more accurate localization of metastatic area(s) in enlarged nodes will improve biopsy results.
(2) determination of presence and location of small metastatic nodes, will improve accuracy of laparoscopic and laparotomic lymph node dissection.
(3) due to higher accuracy of biopsy and surgical node dissection, there may be a shift from laparotomic towards laparoscopic node dissection and towards biopsy, which is less invasive for the patient and less costly.

Future prospects

In the future only one post-USIOP examination will be sufficient to make an accurate diagnosis. Low SI normal nodes can be clearly separated from metastases on both post-USIOP 3D T1-weighted and high resolution T2*-weighted sequences without comparing to pre-contrast images. A node is metastatic if on both sequences there is an area with absence of low SI.

As is the case in MR imaging of the liver using 'double contrast', lesion conspicuity may be improved using a combination of USIOP-infusion and bolus-injection of Gd-contrast.

Conclusions

This prospective study in 59 patients with PC or UBC shows that USIOP is well tolerated, and that post-USIOP MRI significantly improves sensitivity, accuracy and negative predictive value of nodal staging (respectively from 52% to 91%, 75% to 92% and 74% to 94%).

In nine of 11 patients thanks to USIOP MRI small metastases (7–3 mm) in small (<8 mm) lymph nodes were detected, which has very important clinical consequences.

USIOP MRI may be performed using only a combination of two sequences: a 3D T1-weighted, and a high resolution T2*-weighted sequence.

Further multicentre studies to reproduce these results are promising and necessary.

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