15 Use of Dynamic Contrast-Enhanced MRI in Multi-Centre Trials with Particular Reference to Breast Cancer Screening in Women at Genetic Risk

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CONTENTS

15.1 Introduction

This chapter considers issues concerned with developing multi-centre trials using dynamic contrast-enhanced MRI studies. As techniques have been considered in other chapters, emphasis is placed on issues that relate to trials, and particularly their implementation across centres. Both diagnostic and therapeutic trials are considered, although as yet most experience arises from diagnostic trials. Trials that have been reported are considered, and the UK study of magnetic resonance as a method of screening women at genetic risk of breast cancer (MARIBS) using dynamic contrast-enhanced MRI is taken as an example. Issues of organisation, instrumentation, quality assurance and analysis are considered.

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15.2 Multi-Centre Trials

15.2.1 New Diagnostic Techniques

Development and evaluation of new techniques often occurs initially at single centres. Where new approaches are developed at a university or hospital, the centre evaluating the technique is often the same centre that developed the approach. This has the benefit of maximising the expertise in the technique, and is often an essential part of the interactive process of developing and optimising a new clinical technique. Those involved are likely to be advocates of the approach, and the utility established in such a single-centre evaluation may not be representative of the effectiveness of an approach across a range of centres. Manufacturers may also initially pilot a new approach at a single centre, in this case because of the strong continuing interaction required to optimise development. Such a strong interaction allows resources to be focussed, and may lead to scientific publications, assisting the manufacturer's role in alerting the community to new methods and equipment. Often this preliminary stage is then followed by a stage of more widespread evaluation, defining the role of the technique at a number of centres

representing the range of clinical applications and potential purchasers, in some cases leading to further modifications in the technique.

An important issue affecting many preliminary studies is that the clinical conditions examined may not be representative of the final target group. One example would be testing diagnostic methods that might be used for screening for breast cancer on symptomatic patients with more advanced disease than would be typical of a screening population. While this is a reasonable approach in defining utility for more advanced disease, and in developing a technique, it is important to ensure that data obtained for one purpose are not inappropriately utilised to infer utility for more demanding applications.

15.2.2 Multi-Centre Evaluation

While these initial single-centre studies may define the potential utility of a technique, increasing emphasis is being placed on defining the impact of new technologies and approaches on healthcare outcome in the target group. This type of study often requires multiple centres to provide the numbers required for statistical power, and also ensures a representative evaluation of the technique, with a range of expertise more typical of clinical practice. Identification of impact on outcome (and definition of any associated morbidity) is central to evaluating the clinical impact, which may not be directly determined from the immediate diagnostic value.

Although there are many examples of diagnostic evaluation studies, for example comparison of different diagnostic modalities, being performed within a single centre, an objective assessment often has to be built on evaluation of several such studies. These studies may still be influenced by advocacy of a particular technique, and are unlikely to provide as robust an evaluation as a formal multi-centre evaluation.

Screening studies are a particular example of a question that usually requires data from multi-centre studies to define utility. Not only is symptomatic disease often not representative of screen detected disease, in many applications the prevalence of the disease in the screened population is low, requiring large studies to establish a significant result. The studies set up to evaluate the efficacy of breast cancer screening using X-ray mammography provide an example of the complexity of such studies, and identify some of the issues involved in multi-centre trials (Moss and Chamberlain 1996; National Institutes of Health Consensus Statement 1997). While this form of screening clearly identifies women at an earlier stage than would otherwise be the case, the impact on health outcome remains a matter for debate, in part due to the morbidity arising from the radiotherapy treatments used during the period covered by the studies.

15.2.3 Therapeutic Trials

Early stage clinical trials of new therapies have traditionally been carried out at single centres (Phase I/II). Recently Phase I trials have begun to include hypothesis testing elements, rather than concentrating on toxicity and establishing maximum tolerated doses. With these changes there is interest at pharmaceutical companies in performing such studies at two centres, to aid recruitment and provide increased experience. With novel approaches in cancer therapeutics, where treatment may increasingly be tailored to the individual's genome, there may be an increased need to broaden the base, and therefore catchment, of such trials. This trend may develop with other diseases where there is considerable individual variation. Phase III trials are multicentre, requiring coordination and agreed standards across centres. To date, in cancer, these trials have generally used solid tumour volume response as the radiological endpoint, graded using WHO or RECIST criteria (Miller et al. 1981; Therasse et al. 2000). In these studies there has been little cross-site quality assurance or diagnostic protocol standardisation. New therapeutic agents may lead to tumour stasis, but may have other effects on tumour metabolism or function that can be detected by MRI. One example is the effects of anti-angiogenic or anti-vascular treatments, where MR dynamic contrast agent measurements have shown particular promise in demonstrating drug action. Multi-centre studies using these approaches will require much greater standardisation and quality assurance than has hitherto been necessary. Applications of MR to assessing therapeutic response in breast cancer have recently been reviewed (Leach 2002) as has the use of MRI to evaluate angiogenic changes (Leach 2001). The potential for using MRI to assess response in clinical trials has also been evaluated (Harms 2001; Julian 2001).

15.3 Dynamic Contrast Agent Studies

15.3.1 T1-Weighted Methods

Contrast agents used with MRI have predominantly been based on gadolinium chelates, providing a positive contrast on T1-weighted images. Their initial application was to demonstrate areas of blood–brain barrier breakdown, as a method of identifying and classifying CNS lesions such as those from multiple sclerosis, or from cancer. More recently in cancer their use has extended to the evaluation of other solid tumours, aiding discrimination of active disease from fibrosis, necrosis and normal tissues. They are used in other applications to identify perfusion defects, and to increase the sensitivity of MR angiography. In tumour studies, in addition to morphological assessment of the enhanced region, there has been interest in evaluating the dynamics of contrast uptake and wash out, which can be related to physiological parameters by the use of appropriate physiological models.

Initially observations were related to the shape of the uptake and washout curve obtained from a region of interest (Kaiser and Zeitler 1989), from a time series of T1-weighted images, using this as an additional radiological descriptor (Heywang-Köbrunner 1990; Kuhl et al. 1999). This has been shown to be of particular value in breast cancer diagnosis and assessment. Both descriptive and calculated parameters have been developed to characterise these curves (Tofts et al. 1999). More recently there has been interest in deriving physiological parameters, firstly by fitting the curve from a region of interest to an appropriate model (Tofts and Kermode 1991; Hittmair et al. 1994; Tofts et al. 1995; 1999; Kuhl et al. 1999), and then by performing pixel-wise fitting of a time series of images to a model. This leads to the calculation of maps of the parameters generated by the fitting process (Knopp et al. 1994; Parker et al. 1997, 1998; Hayes et al. 2002). Applications of these maps include identification of areas of abnormality, characterising heterogeneity in tumours, assessing response to treatment. Parameters include K^{trans}, which reflects perfusion and vascular permeability, and extracellular, extravascular volume (v_e) (Tofts et al. 1999). In some cases similar techniques may provide information on vascular volume (Li et al. 2000; Zhu et al. 2000). Parameter maps give rise to the question of how best to analyse such information, and how to relate several different parameters, that may be generated in the same study.

While descriptive parameters from T1-weighted images have been shown to be helpful, they are not readily transportable, and are affected by a range of factors including specific sequence parameters, instrumental parameters, inherent tissue T1 relaxation times, built in image processing. These can vary markedly between MR systems, and some may vary with hardware and software revision, or routine maintenance. Thus there are significant problems to be addressed in generalising such techniques across several centres for multi-centre trials.

Analysis methods based on model fitting require the concentration of contrast in the tissue to be calculated. This involves certain assumptions, such as the relaxivity of the contrast agent in plasma, and is calculated either based on an assumption that T1 relaxation change, and hence contrast agent concentration, is proportional to the change in signal intensity; or more accurately is based on methods that directly measure T1 relaxation time. The former approach is liable to bias between tissues having different intrinsic T1 relaxation times, as well as from non-linearities between T1 relaxation change and signal intensity. Application of such techniques to multi-centre trials also requires considerable attention to transferability and quality assurance, but this is aided by the considerable analysis and evaluation required to implement such techniques.

15.3.2 T2*-Weighted Methods

Assessment of the first-pass bolus of contrast agent, resulting in transient susceptibility changes close to capillaries, as the bolus passes, and resultant loss of signal in areas of perfusion on T2*-weighted images, provides further information on local blood volume and perfusion (Ostergaard et al. 1996). This has been shown to be of value in differentiating benign from malignant breast lesions (Kuhl et al. 1997; Kvistad et al. 1999). This technique has been used to evaluate regional brain perfusion and blood volume, and more recently has been applied to the study of extra-cranial tumours. The technique demands high temporal resolution, ideally 1–2 s per time point, so it has usually not been associated with methods evaluating K^{trans}. However, recently several approaches combining both T1-weighted and T2*-weighted imaging to obtain a wider range of parameters that characterise tumours have been reported (Baustert et al. 1998; Barbier et al. 1999; Vonken et al. 2003). These techniques are also being employed to assess

response to treatment. As yet there are no reports of the techniques being applied in multi-centre trials, but the general principles are similar to those for T1-weighted studies.

15.4 Current Multi-Centre Studies Using Dynamic Contrast-Enhanced MRI

15.4.1 Breast Cancer

Although a number of multi-centre studies of breast cancer diagnosis or screening are in progress using dynamic contrast agent MRI, few have published details of the protocol and methodology to be employed. Heywang-Köbrunner et al. (2001) have reported a trial conducted at 11 centres using Siemens 1.0-T or 1.5-T scanners to improve standardisation and optimise interpretation guidelines for dynamic contrast-enhanced MRI. This study employed an 87-s 3D fast low-angle shot (FLASH) sequence repeated once before and five times after a standardised bolus of 0.2 mmol Gd-DTPA/kg. Imaging findings were correlated retrospectively with histopathology in 512 histologically correlated lesions. By setting specificity thresholds of 30%, 50% and 64%–71%, sensitivities of respectively 98%, 97% or 96% at 1.0 T and 96%, 93% and 86% at 1.5 T were reported. The best results were obtained by combining up to five wash in or wash out descriptors.

The UK study of contrast-enhanced magnetic resonance imaging as a method of screening women at genetic risk of breast cancer (MARIBS) has published its rationale (Brown et al. 2000b), study protocol (Leach 1997; Brown et al. 2000c) and radiological measurement and assessment protocol (Brown et al. 2000a). Much of this has also been included in a report of the International Working Group on Breast MRI (1999) which includes details of other studies in progress at the time of the report. The MARIBS protocol is also summarised in a review of MR in breast screening (Leach and Kessar 2002) and in a recent update reporting progress to date and comparing reported detection rates in similar studies (Leach and MARIBS Advisory Group 2002).

Kuhl and colleagues (2000; Kuhl 2003) have reported initial results from a trial of MRI screening in women diagnosed as or suspected of carrying a breast cancer susceptibility gene. This is a single-centre study, and together with other similar single-centre studies is reviewed in Leach and MARIBS Advisory Group (2002).

A further study is applying and evaluating a method of breast cancer diagnosis based on the use of three time points (the 3TP method) (Furman-Haran et al. 1998; Weinstein et al. 1999). Recently a multi-centre study of breast cancer screening has commenced at nine centres in Italy (Podo et al. 2002), with 102 participants recruited so far. The study includes participants at 1 in 2 risk of being mutation carriers, from age 25 (women) and 50 (men) with no upper age limit, and includes individuals with a previous history of breast cancer. Imaging is based on T1-weighted 3D spoilt gradient echo images acquired coronally or axially with a matrix of 128×256 coronally. MRI is compared with X-ray mammography and ultrasound. Out of 119 screening measurements, eight cancers have been detected, with five being invasive ductal or lobular, and three being ductal or lobular cancer in situ. Five of these occurred in patients with a previous history of breast cancer. Of the eight cancers detected, only one was seen on X-ray mammography and ultrasound.

Multi-centre studies investigating dynamic contrast-enhanced MRI in breast cancer may be divided into those considering morphological features alone, those considering dynamic contrast alone and those considering both morphology and contrast enhancement. This classification aids consideration of aspects important for multi-centre trials.

The use of the morphological features of tumours, observed on contrast-enhanced MRI images at specific times following injection, to determine a diagnosis was introduced by Heywang and colleagues (1986). Similar approaches, in some cases utilising fat suppression techniques, have been used in a number of studies (Harms et al. 1993; Allgayer et al. 1993; Fischer et al. 1993; Greenstein Orel et al. 1995; Tesoro-Tess et al. 1995; Orel 2000) showing high sensitivity (88%–100%), but often lower specificity (37%–89%). While early studies used 2D imaging techniques, more recent work has used 3D imaging sequences, in several cases accompanied by interleaved alternate breast imaging (requiring switching of coil elements to maximise sensitivity), which allows smaller fields of view, optimising acquisition time and spatial resolution (Greenman et al. 1998). 3D techniques have intrinsically longer acquisition times than 2D approaches, but allow all of one (or two) breasts to be assessed, of particular importance in diagnostic assessments and in screening.

The measurement of the shape of the contrast curve obtained from an ROI was introduced by Kaiser and Zeitler (1989), and has been widely used (Heywang-Köbrunner 1990; Kuhl et al. 1999). It provides strong independent diagnostic power. Using simple descriptors of the shape of the wash-out curve. Kuhl and colleagues (1999) in Bonn have reported a sensitivity of 91% and specificity of 83% for cancer detection. Time resolution varies, from about 10 s or less for single-slice approaches to 90 s for 3D volume measurements (Orel and Schnall 1999; Brown et al. 2000b). Initial studies have used curves derived from regions of interest (ROI) for analysis, allowing a number of empirical descriptors of the contrast curve to be defined (Kuhl et al. 1999; Brown et al. 2000b). More sophisticated approaches use model fitting, in some cases accompanied by quantitative imaging approaches, either on an ROI basis, or calculated pixel by pixel.

Many investigators combine the information from morphology and contrast kinetics. Greenstein Orel and colleagues (1994) in Philadelphia reported on this approach in 1994, showing that addition of morphology to kinetic data improved discrimination of benign and malignant disease. Morphology is particularly helpful in discriminating fibroadenoma, some of which demonstrate tumour like contrast kinetics. The MARIBS study (Brown et al. 2000b) includes a primary 3D screening assessment, with 90 s time resolution, allowing both dynamic and morphological assessment. Equivocal cases are recalled for a further high-time-resolution 2D imaging study to provide higher-time-resolution dynamic data to aid specificity.

Morphological parameters are recorded based on a predetermined set of descriptors, as is the spatial pattern of contrast uptake (Brown et al. 2000b). The shape of the contrast curve is similarly described, and several qualitative parameters are calculated to describe contrast wash-in. All of these factors are assigned scores which are summed to give a numerical estimate of likely malignancy. A diagnostic decision is based on the radiologist's experience rather than the score, which is currently being evaluated in a symptomatic cohort. All MR results are double read blind, as are the comparison X-ray mammograms. This standardisation of reporting is an important aspect of the standardisation required for a multi-centre trial. Recently the International Working Group on Breast MRI has used a similar but more detailed categorisation of morphological and dynamic features to develop a lexicon of MR descriptors for diagnostic reporting (International Working Group on Breast MRI 1999; Ikeda et al. 2001), which will be helpful in future studies.

15.4.2 Multi-Centre Trials in Other Conditions

Barkhof et al. (1997) have considered the requirements for multi-centre trials in multiple sclerosis, identifying the need to establish observer variability over multiple centres, as well as improve quantification methods and compare the different techniques in a multi-centre longitudinal fashion in order to include variation caused by both scanner and segmentation techniques, in addition to biological activity. Barkhof et al. (1993) report a database developed for recording serial brain MRI results suitable for multiple sclerosis multi-centre trials. Nyland et al. (1996) report on a randomised, double-blind, placebo controlled multi-centre study at eight centres in Norway to evaluate the efficacy and safety of 4.5 and 9.0 MIU recombinant human interferon alfa-2a (Roferon-A) given thrice weekly in patients with relapsing-remittent multiple sclerosis. The primary objective is to determine new disease activity analysed by monthly MRI with gadodiamide (Gd-DTPA-BMA, Omniscan).

Parodi et al. (2002) have investigated the intra- and inter-observer agreement variability of a locally developed Growing Region Segmentation Software (GRES), comparing them with those obtained using manual contouring (MC) in MS lesions seen on proton-density-weighted images (PDWI) and on Gd-DTPA-BMA enhanced T1-weighted images. The authors report that the intra- and inter-observer agreements were significantly greater for GRES compared with MC ($p<0.0001$ and $p=0.0023$, respectively) for PDWI, while no difference was found between GRES an MC for Gd-T1WI. The intra-observer variability for GRES was significantly lower on both PDWI ($p=0.0001$) and Gd-T1WI ($p=0.0067$), whereas for MC the same result was found only for PDWI ($p=0.0147$). These data indicated that this implementation of GRES reduces both the intra- and the inter-observer variability in assessing the area of MS lesions on PDWI and might prove useful in multi-centre studies.

A number of multi-centre studies have reported on the utility and acceptability of contrast agents (for example Aslanian et al. 1995, 1996; Wang et al. 1997; Saini et al. 2000). Although these studies require a degree of standardisation, they do not employ dynamic contrast analysis and are aimed at dem-

onstrating efficacy of the contrast agent rather than addressing a diagnostic or therapeutic question.

Several multi-centre studies have examined the utility of ^{1}H magnetic resonance spectroscopy for the diagnosis and evaluation of brain tumours (Sijens et al. 1995; Negendank and Sauter 1996; Negendank et al. 1996), and to examine the neurological complications of AIDS (Paley et al. 1996). This required standardisation of measurement parameters, selection of placement of region of interest, and analysis. A multi-centre study of ^{31}P magnetic resonance spectroscopy is currently in progress (Arias-Mendoza et al. 2000).

15.5 Standardisation and Issues to Be Resolved in a Multi-Centre Trial Design

Taking the MARIBS design as an example, given that more details are available and published than for most other multi-centre trials using dynamic contrast agent evaluation, in this section the major issues to be addressed in trial design are described, together with consideration of their relative importance with respect to single-centre trials. The following section will then consider approaches to tackling each issue.

15.5.1 Defining the Scientific Question and Design

The question posed dictates the trial design, the test required, and the power required of the study. A decision as to whether a study is single- or multi-centre has major implications for design and funding, and is likely to be dictated by prevalence of the condition and likely recruitment at individual centres, the context of the question (for example evidence that a new technique has diagnostic and clinical potential might be addressed at a single centre, establishing that the technique is robust and can be used routinely in a general hospital setting, as a change in practice would require a multi-centre trial), issues of regulation and pharmaceutical licensing, and the level of confidence required by a pharmaceutical manufacturer before committing significant funding to further development or Phase III trials. One or more control arms may be required and comparison of diagnostic tests may be required.

A statistical evaluation to determine the sample size is an essential first step, taking account of the population, likely potential accrual rate, maximum possible measurement or treatment capacity taking account of return visits, estimating drop-out and acceptability of the study design to prospective patients. Poor entry into trials is a major problem, and this may be acerbated by high drop-out in studies that are measurement intensive. Realistic estimates of accrual, and of instrument access, can be difficult to obtain, and in practice are often affected by local or national policy changes during the course of a study. However, good estimates, adequate funding and clear local agreement, are particularly important to multi-centre trials.

15.5.2 Ethical Approval

Approval by the appropriate ethical committees is a prerequisite for any research study. This is an area where multi-centre trials are considerably more complex than single-centre studies. In the UK, until recently, full consideration and approval of a study was required by each local ethical committee involved. For the MARIBS study, this involved many committees, with one individual measurement centre potentially having to submit applications to many local ethics committees if recruiting from a number of hospitals. Recently this system has been streamlined, with the establishment of regional multi-centre research ethics committees (MRECs). If one such committee approves a study, the same protocol has still to be submitted to individual local research ethics committees (LRECs), but they are guided by the MREC decision.

15.5.3 Determining an Imaging Protocol

The imaging protocol must address the scientific question. For dynamic contrast studies the measurement endpoints required will determine the protocol. Issues to be considered include:

- Is morphology required, what image weightings are required for any non-contrast aspects of the examination (e.g. T2-weighted images), what spatial resolution is desirable (including slice thickness), what FOV is required?
- For the dynamic contrast component, what spatial resolution (including slice thickness) is required, what FOV, is a 3D examination (or complete organ

coverage) required for each time point, what temporal resolution is required?
- For a dynamic study, what type of information is required? This will define the type of sequences to be used.
- The simplest form of study will obtain information before and at a time point after contrast, providing little functional information other than the uptake of contrast. Dynamic studies with time resolutions of the order of 90 s provide information on the change in signal intensity over a number of time points, providing some of the dynamic information characterising washout shape referred to above, and allow a number of qualitative parameters to be defined. These measurements can be made quantitative by incorporating sequences that allow contrast agent concentration to be calculated, allowing these parameters to be put on a quantitative basis, and providing absolute contrast concentration.
- Higher time resolution studies, including sequences designed for quantitative studies, allow the image data to be fitted to pharmacokinetic models of contrast uptake, allowing parameters to be obtained that describe aspects of the tissue physiology, delivery of the agent or descriptors of the contrast kinetics. Time resolutions of the order of 10 s have been used for T1-weighted studies (shorter time resolution has been used in some studies), or approaching 1–2 s for T2*-weighted studies. Many of these studies have used 2D imaging, although as instrumentation improves there is interest in performing 3D measurements.

The final imaging protocol is likely to involve compromises, both in the number and range of measurements, the resolution and volume coverage, and the temporal resolution. In a multi-centre trial, the capabilities and the practicality of implementation at different sites must also be considered.

15.5.4 Equipment Issues

Given an ideal imaging protocol from a scientific point of view, the next issue to be considered is the practicality of implementing it on the equipment available for the study. This should be easiest for a single-centre study, where the investigators are very familiar with the equipment and its capabilities. However, a number of issues still arise, which are a subset of those faced by a multi-centre trial.

15.5.4.1 Issues for Single-Centre Trials

Choice of field strength, imaging coils and patient set up – these must be appropriate to the trial.

Does the manufacturer provide the sequences required for the trial? This may be a particular problem when quantitative measurements are required, or when faster than usual measurements are needed, or when the protocol calls for an unusual combination of information, for example interleaved T1 and T2*-weighted information (D'Arcy et al. 2002). If a non-standard sequence is required the investigators may need to prepare it themselves, with all the required testing and validation. They will need to persuade the manufacturer to implement it, or they will need to transfer it from another academic site (which again may require manufacturer's agreement). To develop and install a sequence (other than for minor modifications) it is likely that the user will require access to the pulse sequence development language and facilities, have staff with the required know-how, and have a degree of support from the manufacturer, usually with a research agreement. Persuading a manufacturer to tailor and provide a non-standard sequence has recently become very difficult, due to the requirements for good manufacturing practice, and satisfying medical equipment regulatory bodies such as the Medical Devices Directorate in the UK and the Federal Food and Drugs Administration in the USA, and legislation such as the EU Medical Devices Directive. Manufacturers are unwilling to commit themselves to doing this, and further are requiring complex legal indemnities to be agreed before transferring such non-product sequences to clinical sites. While clinical research centres may have the expertise and resources to deal with these issues, they present more of a problem (and a drain on staff time) at non-expert centres. This is also an impediment in multi-centre trials, as an academic site producing a new sequence may meet similar risks in transferring sequences, and may also need a contractual framework clearly identifying intended use, limits on liability etc. These barriers to medical research are now significant, and require revision of international medical equipment approval mechanisms to reduce adverse impact on medical research.

The user needs to ascertain whether the equipment will allow the measurements required. One example is a common practice in performing quantitative measurement sequences, where the signal acquisition parameters for a number of sequences are fixed, so that the numbers obtained with one sequence can

be used as a reference for subsequent sequences (e.g. proton density sequences used as a reference for T1-weighted sequences, to allow rapid measurement of T1 relaxation times). Some manufacturers do not support this facility, and automatically reoptimise some or all of transmit amplifier/attenuator settings, receiver amplifier/attenuator settings, receive ADC set up and image scaling factors and filter factors each time a sequence is loaded.

Once the sequences have been defined, if any non-standard processing (other than that provided by the manufacturer) is required, programs may need to be developed and run off-line. Again the user is likely to need access to the image file structure (usually requiring manufacturer's agreement), the image file store on the imaging device, and if the program needs to be run on a separate workstation, the means to export the data in a way that can be read. All of these steps can pose problems, where provision was not made at specification and purchase of the imaging equipment.

Equipment performance may need to be monitored via a quality assurance programme to ensure that equipment performance variation does not introduce unacceptable variance in the measurements, and that the location and conduct of measurements are themselves not the cause of variance.

Users should review routine maintenance and any upgrades of hardware or software critically. It is not unusual for such activities to vary the status of the equipment in a way that adversely affects a clinical study, and upgrades can remove or change sequences in a way that is not advised or expected.

If execution of a study requires any special equipment or software modifications, programs or datasets, the user should ensure that a mechanism for reinstating them on top of the manufacturer's rebuild is available, in the event of, for example, a disc crash or operating system corruption.

15.5.4.2 Issues for Multi-Centre Trials

Multi-centre trials involve all of the above issues, but in addition the issues posed by arrangements and level of expertise at the different centres, the possibility of different equipment and software (model, revision level, manufacturer) have a major impact on the design of, and requirements to support, trials.

In all cases there will be a need to ensure that staff are trained in the protocol and in the analysis of the data, including use of any specialised software. Equipment will need to be assessed to ensure comparable performance at the different centres, and over time. It is advisable to have a central quality assurance resource, that will monitor equipment performance, and diagnostic performance, during the study. This will help identify and resolve potential problems, thereby improving the quality of the study.

15.5.4.2.1 Studies with Equipment from One Manufacturer

A number of multi-centre diagnostic trials have been designed using equipment from one manufacturer. Examples include the evaluation of dynamic contrast breast MRI (Heywang-Köbrunner et al. 2001), and a study examining ^{1}H MRS in the brain (Negendank and Sauter 1996). Usually single-manufacturer studies reduce the problems attached to sequence selection and provision, and to data sharing and transfer for analysis. Significant issues may remain if different models or releases of equipment and software are involved. Support by the manufacturer for the protocol and study can considerably reduce the burden on the study co-ordinating centre. However the investigators should remember that scientific responsibility resides with them and that despite their best intentions, manufacturers can make mistakes. The investigators need to confirm that sequences and analysis programs do perform as intended.

15.5.4.2.2 Studies with Equipment from Several Manufacturers

Fewer studies have used equipment from multiple manufacturers, including detailed analysis and quantitative approaches. Two examples are the MARIBS study (Brown et al. 2000b,c) and the multi-centre study of ^{31}P MR spectroscopy in cancer (Arias-Mendoza et al. 2000) which has involved advanced decoupled spectroscopy including extending the instrumentation routinely available. An international workshop reported on requirements for standardisation of measurements using magnetic resonance spectroscopy (Leach et al. 1994). When equipment from different manufacturers is used, it is important to ensure that the planned protocol on each instrument is as close as possible to the imaging protocol for the study. This can require considerable understanding of the peculiarities of each instrument, and it is advisable for an expert in each type of hardware to be available to the study. Often descriptors and adjustable parameters vary between machines, and there may not be a one to one relationship. The closest approximation must

be identified, taking into account the implications of changes made to sequences. There may be differences in the way sequential repetitions of sequences can be run, and the results stored (of importance in dynamic contrast measurements) and there may be other issues affecting relative normalisation of sequence set-up (as discussed above).

Analysis and data storage may vary between manufacturers, including the ability to store regions of interest, contrast uptake curves, and the capability to regenerate them if required. It may be necessary to transfer data between sites, or to common independent processing software at the user site, or to a co-ordinating centre. Access to transfer routes, and information on the data structure, can be an issue. A central coordinating site is unlikely to have close working arrangements with all manufacturers, requiring some issues to be solved by a lead site for a given manufacturer.

The image information from different manufacturers may (and does) vary. Issues include different image scale factors, leading to different apparent enhancements between manufacturers, which can give manufacturer-dependent ranges for empirical pharmacokinetic parameters; different image processing and filters, which may or may not be accessible to the user; different number ranges and ADC set-up. Analysis and evaluation protocols need to take account of these issues.

Suitable quality assurance protocols and calibrations will be required to address these issues.

15.5.5 Data Analysis

In addition to ensuring that data are obtained in a consistent way and identifying and addressing differences between equipment, it is necessary to determine how the data are to be evaluated.

Morphological information may be assessed by normal radiological review. However, a consistent and robust reporting is required, and it is likely that this may need to be recorded in an evaluable form. It is therefore desirable to establish terminology, and the importance attached to given characteristics, at the outset. Often, if the technique is new, experience will be limited, and independent double reading, together with some independent quality assurance process, will be advantageous.

If dynamic data are to be obtained from a region of interest, criteria for selecting a region, and parameters to be assessed or measured need to be established.

If pixel-wise calculation of empirical or quantitative parameters is to be performed, this needs to be done in a consistent and robust way, with identification of any assumptions or approximations. The methods of analysing these parameter maps have to be defined and applied consistently, with appropriate quality assurance.

Provision for retaining and backing up the data, together with ensuring confidentiality and security need to be established.

15.5.6 Publication Policy

It is advisable for multi-centre studies to have a publication policy to define authorship issues at the outset.

15.6 Addressing Issues in Multi-Centre Trials Using Dynamic Contrast Agents, with Reference to the MARIBS Study

Based on the issues identified above, the approach taken in the MARIBS study is described, as an example.

15.6.1 Scientific Question and Study Design

The study was designed to address the question of whether dynamic contrast-enhanced MRI was superior to X-ray mammography in detecting and diagnosing breast cancer in women at high genetic risk. The target group was women below the age of 50, where X-ray mammography has limitations. Based on the estimated sensitivity of MRI (based on symptomatic studies) and X-ray mammography in this age group, it was originally estimated that some 1500 women at 50% risk of carrying BRCA1, BRCA2 or TP53 gene mutations needed to be accrued. This meant adopting a comparative rather than randomised trial design, as this type of design required the smallest numbers, due to the relatively small number of known mutation carriers. However, this also meant that mortality could not be used as an endpoint. The statistical basis for the trial design has been reported (Brown et al. 2000c). This accrual required a multi-centre design to accrue sufficient women, and to provide

sufficient imaging capacity. It also was necessary to use a range of MR imaging equipment and manufacturers, to take account of instruments available at the different recruiting centres. Some 22 genetics and MRI centres are contributing to the study. In the event, due to limitations in recruitment at genetics centres, and availability of imaging resources, the overall accrual has been reduced to 950 women and a total of 3300 scans, which should detect a difference between X-ray mammography and MRI at the 1% significance level with 70% power, and at the 5% significance level with 90% power (Leach and MARIBS Advisory Group 2002).

15.6.2 Ethical Approval

Based on the protocol, approval was sought originally at the Royal Marsden Hospital Research Ethics Committee, and subsequently at all referring and imaging centres. Due to changes in requirements, and later recruitment of some centres, multi-centre ethics approval was also obtained from the North Thames Multi-Centre Research Ethics Committee (MREC).

15.6.3 The Imaging Protocol

The objective of the study was to investigate dynamic contrast-enhanced MRI in comparison with the standard technique of X-ray mammography. As a screening investigation it was necessary to evaluate both breasts, maximising the sensitivity for detection of small lesions, whilst providing adequate resolution to define them. This implied using dedicated breast coils and a field strength of 1.0 T or 1.5 T. In order to maximise sensitivity, a double dose (0.2 mmol/kg of Gd-DTPA) of contrast was used, delivered by bolus injection (about 10 s). In addition to maximising sensitivity, it was important to optimise specificity, to minimise unnecessary follow-up or biopsy. This suggested including both morphological and dynamic evaluation, maximising spatial resolution to improve structural definition, and minimising time resolution to improve characterisation of the contrast dynamics. The protocol therefore includes high-resolution 3D scans prior to and after the dynamic contrast sequence (0.89*0.66 mm resolution) and a lower resolution dynamic 3D sequence before and after contrast (1.33*1.33 mm resolution), both with 2.5-mm slice thickness. The lower resolution 3D sequence provides dynamic enhancement information with a time resolution of 90 s, in line with much published information on using dynamic contrast uptake curves as a discriminant in breast cancer diagnosis. Images are taken in the coronal plane to minimise the sequence duration for a given field of view by allowing an asymmetrical field of view. The dynamic T1-weighted sequence is preceded by a proton density sequence with identical timing but a 6° rather than 35° flip angle. This allows T1 relaxation times for tissues before and during contrast enhancement to be calculated. Figure 15.1 shows the full set of image data in an example of a screen detected cancer. Figure 15.2 shows a graph of the dynamic uptake curve obtained in regions of interest in fat, parenchymal tissue and tumour. This protocol could be applied with little modification to a wide range of 1.0 T and 1.5 T instruments, although high-specification instruments could have employed better time resolution or obtained higher resolution.

While the above (Visit A) protocol provided the primary screening measurement, it was recognised that the 90-s time resolution might limit the specificity of dynamic contrast measurements. Where findings were equivocal, a second visit 2 weeks later (Visit B) would be performed. This was designed to provide higher temporal resolution in equivocal lesions, providing 10-s time resolution for 2D slices through lesions of interest. The protocol contained the same pre- and post-contrast high-resolution 3D images, but now uses a 2D sequence with up to five slices, preceded again with a proton density sequence for the same slices, to follow the dynamic contrast uptake. Again the protocol could be implemented on a wide range of scanners. The full protocol for both visits has been published (Brown et al. 2000a).

15.6.4 Quality Assurance

To ensure that the sequence operated accurately, and provided the correct contrast, a quality assurance protocol was devised. This incorporates a routine QA measurement to be performed on a phantom provided to the centre, that is tailored to fit within the specific breast coil at that centre. This contains a material of known T1 relaxation time and allows T1 relaxation time, signal to noise, and coil homogeneity to be measured (Hayes et al. 1998, 1999).

An additional more detailed test assessment has been designed to be conducted by a study physicist

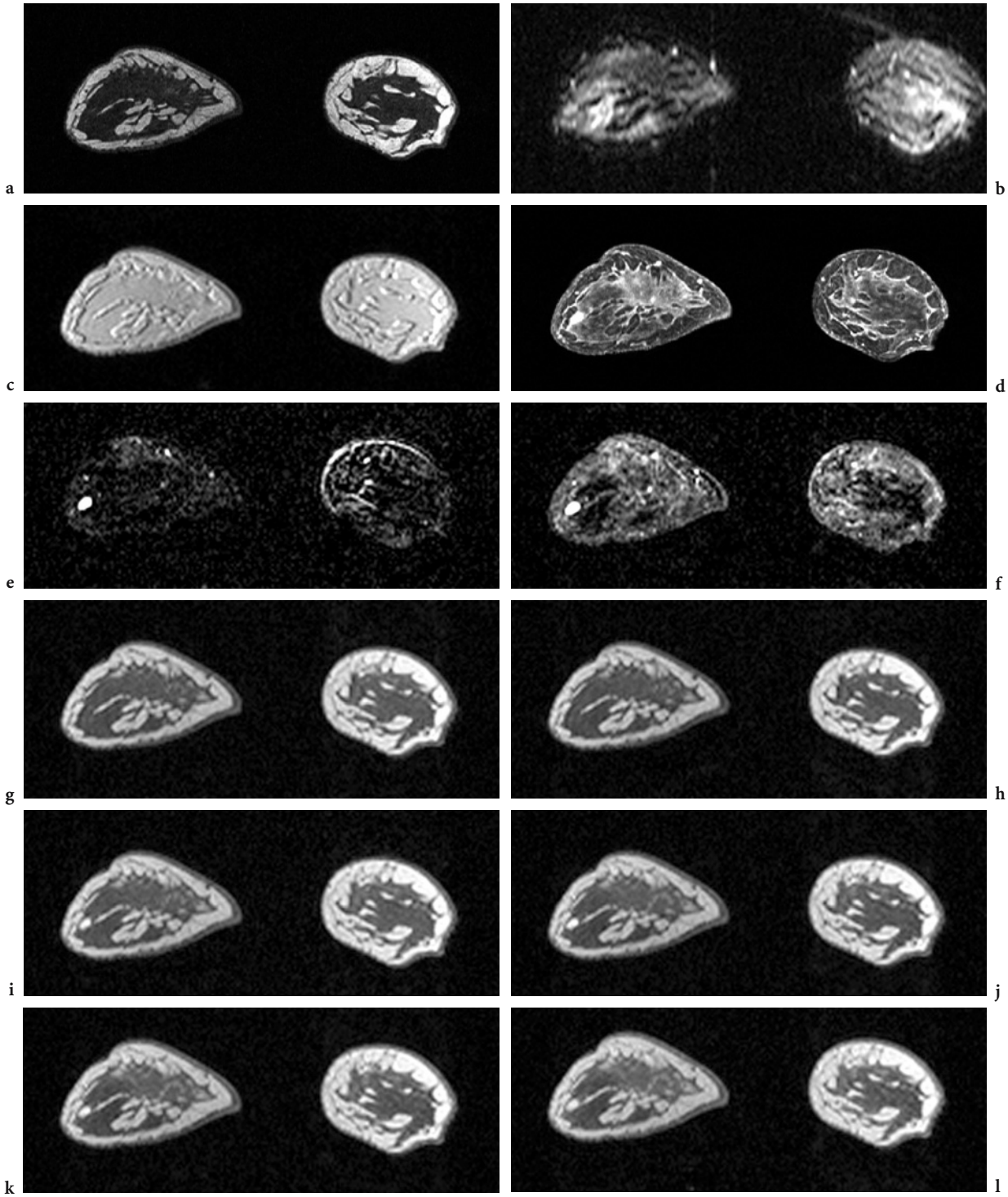
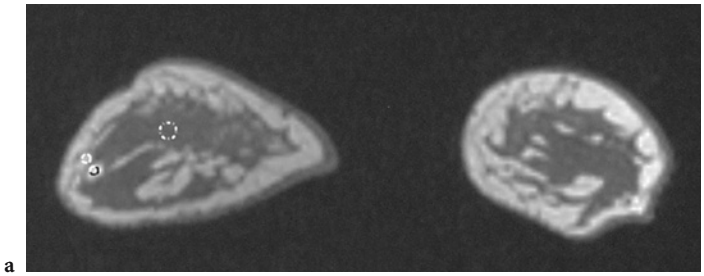
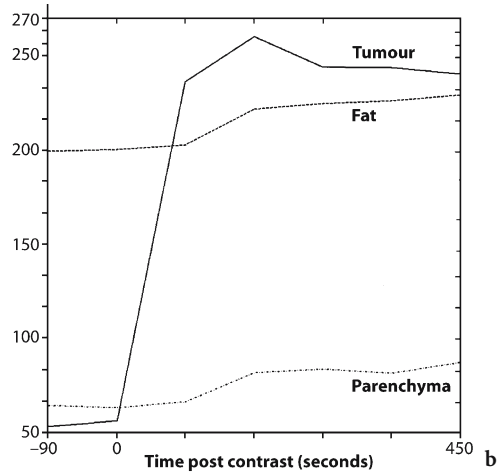


Fig. 15.1a-l. Images from the "Visit-A" screening protocol from a 35-year-old woman with an MR screening detected lesion considered suspicious on the Visit-A scans. A subsequent "Visit-B" scan confirmed a suspicious time intensity curve and cytology following a fine needle aspirate confirmed carcinoma. Images show the initial high-resolution T1-weighted scan (**a**, pre-contrast T1-weighted high resolution); a T2-weighted image (**b**, T2-weighted); proton density-weighted image (**c**, proton density-weighted); six of the seven dynamic contrast images at 90-s intervals (starting at –90, 0, 90, 180, 270, 450 s, with contrast commencing at 0 seconds) (**g–l**, 1st–5th dynamic, 7th dynamic), the post-contrast high-resolution fat suppressed image (**d**, T1-weighted fat-suppressed post-contrast), early subtraction image (180–0 s) (**e**, early subtraction), late subtraction image [450 s (–90 s)] (**f**, late subtraction)



a



b

Fig. 15.2ab. a Selected regions of interest shown on the 3rd dynamic post-contrast image selected in tumour, parenchyma and fat in the patient shown in Fig. 15.1. **b** Signal intensity versus time curves for the three selected regions

after installation of the study sequences, twice yearly thereafter, or after equipment upgrades or modifications. This includes T1 measurements, checking the contrast response of the sequences and providing T1 calibration curves to allow the quantitative measurements to be corrected for the effects of slice profile. In addition, slice profile is measured, together with spatial resolution.

These quality assurance tests aim to strike a balance between ensuring each MR system is performing the protocol properly, by periodic detailed assessments; providing a routine check on performance to alert local staff and the coordinating centre to any problems; and avoiding undue time on the equipment. Some centres, particularly those with no active developmental research, have difficulty scheduling these QA sessions, a problem that could be reduced with more explicit funding of machine time.

15.6.5 Implementation of Sequences

The sequences used in the study were implemented on the Siemens Vision 1.5-T MR system at the Royal Marsden Hospital, Sutton, by modifying standard sequences, and tested extensively. The sequences were modified to run on 1.0-T Siemens systems, with the help of the manufacturer who installed them at non-research sites. Standard sequences were modified for GE sites, again with some support from the manufacturer. Standard sequences were available for Philips systems, although additional steps were needed to provide calibration between proton density and T1-weighted images, this being applied at the processing stage. Again the manufacturer provided support for this. The sequence was also implemented on a Marconi scanner, with support from the company. One of the aims of this study was to use sequences that were transferable and close to standard sequences.

For some multi-centre studies using dynamic contrast agents, it may be desirable to use more advanced approaches, that may not be closely based on a standard sequence. In such cases it will be necessary either to base the studies at capable research sites with the capability and explicit funding to implement the approach, or to ensure that the study uses similar systems such that pulse sequences and processing are directly compatible. Alternatively, a major process of securing appropriate manufacturer's support (to an agreed timetable) will be required, which may require influence greater than that wielded by an individual academic research centre. Currently the US NCI is considering reaching such agreements with manufacturers, and funding the necessary costs, to attain objectives that are not otherwise practicable.

15.6.6 Equipment Issues

Many issues relating to different manufacturers' equipment have been discussed above and addressed in sequence design and in pulse programming. A number of equipment issues can have an important bearing on the quality of measurements. In the MARIBS study, the major determinants in selecting equipment were that there should be a dedicated breast coil, that the field strength should be 1.0 T or 1.5 T, that the system should have shielded gradients.

The latter requirement was an important determinant of image quality and speed. For many dynamic contrast studies, uniformity of the transmit coil will be important, as this can affect the measured signal intensity, and adversely affect quantitative measurements. Assessing this over the area to be imaged is an important part of quality assurance and validation.

Generation of slice-selective pulses often varies between manufacturers, and may also show relative changes with slice thickness. It is advisable to assess this, and ensure that evaluation takes account of it. A relatively poor slice profile will reduce the contrast of T1-weighted images, compared with systems having a better slice profile, thereby reducing contrast sensitivity. Gradient amplitude, slew rate, gradient screening, eddy current corrections and imaging coil design (which can provide a source of unshielded eddy currents) can affect both the speed of equipment and the quality of images, and should be assessed by standard quality assurance tests. High transmitter power can allow shorter RF pulses, which may benefit imaging speed.

The receive chain, including the way the ADC is normalised, the properties of in-line filters, and the use of image processing, can vary widely between manufacturers, and should again be controlled for in multi-centre studies.

Data formats and the media available for recording data are another major source of incompatibility between systems. Although DICOM in principle provides a format that should translate, in practice this may only be available on certain output routes, which may not be those most convenient for a multi-centre trial. It is likely that a capability to read the internal file formats of different systems will be required, which may require agreements with manufacturers. This is a specific problem it was necessary for us to overcome in the MARIBS study, and we are grateful to the manufacturers for their support in achieving this. Processing software from manufacturers also varies widely, and if this is to be used, care needs to be taken to ensure that it works as described and that the users understand the description. Some standardisation may be required to allow for different gain factors, or image value offsets between manufacturers. It is also important to check for dynamic studies that the software is correctly identifying the timing of sequences. While manufacturers are beginning to introduce analysis packages for functional MR information, these are likely to depend on particular acquisition strategies, and may not translate well to a trans-manufacturer trial.

15.6.7 Data Analysis

Many of the issues to be considered have been dealt with above. Double reading, blinded to the first reader, and ideally at another centre, has been included in the MARIBS study. This provides a variety of checks on the process and is recommended. Investigation of problem cases and a random sample of cases is also undertaken by the MARIBS study radiologist, and is recommended. In the MARIBS study, a symptomatic cohort has also been evaluated, providing additional experience to radiologists, and providing for a separate evaluation of the radiological process. A quality assurance evaluation is in process, circulating complete data sets to the participating radiologists. Separate test cases have been prepared for radiologists familiar with different machines. A quantitative analysis of study data, allowing comparison with the empirical analysis conducted at each centre, is planned, and will provide an interesting comparison, as well as, in principle, more standardised data. This approach is likely to be necessary in studies monitoring new anti-angiogenic or anti-vascular agents.

15.7 Conclusions

Dynamic contrast-enhanced MRI methods provide a powerful tool for detection, diagnosis and evaluation of several diseases. They have a growing role in the assessment of therapies, particularly new treatments directed at vascular processes. While much has been achieved in developing and demonstrating techniques, with the continuing advances in instrumentation, there is clearly room for considerable further development. For these applications to have widespread use there is a need for further academic development, and the support from manufacturers, regulators, pharmaceutical companies and research funding organisations to support implementation of techniques across different platforms.

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