MAGNETIC RESONANCE IMAGING
IN THE STAGING AND TREATMENT OF
BREAST TUMOURS

Thesis submitted to the
University of London for
the degree of
Doctor of Philosophy (PhD)

by
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1997

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ABSTRACT

Conventional X-ray mammography is the imaging modality most commonly used to diagnose breast cancer. However, there are limitations to its accuracy for assessing the locoregional extent of disease, the diagnosis of suspected tumour recurrence within the breast, and assessment of response to neoadjuvant treatment. Locoregional disease staging is important as it affects the choice of treatment and ultimately clinical outcome.

Breast-conserving surgery has been developed to improve the cosmetic results of an otherwise deforming surgery. It is widely accepted to be a safe option in selected patients when coupled with appropriate adjuvant treatment. Preliminary experience with interstitial laser photocoagulation (ILP) as a minimally invasive treatment of primary breast cancer has shown promise, but the technique has lacked a suitable imaging modality to demonstrate the treatment effects.

Within this thesis, there are two major themes. The first explores whether magnetic resonance (MR) (a non-ionising imaging modality with an intrinsic high soft tissue contrast and spatial resolution) is of value in addressing the limitations of X-ray mammography. The second theme explores ILP as a means of percutaneously ablating benign and malignant breast tumours, and to develop MR imaging to monitor the response to therapy.

The results have shown an overall improved accuracy of contrast-enhanced MR imaging compared to mammography in (a) the local staging of primary breast cancer with regards to invasive tumour size measurement, multicentricity, detection of extensive intraductal component, assessment of nipple-retroareolar involvement with tumour, and axillary node metastases, (b) the diagnosis of local tumour recurrence and, (c) the assessment of residual disease after neoadjuvant therapy.

In the studies evaluating ILP, techniques enabling larger diameter of tissue necrosis to be achieved were developed allowing in some cases complete ablation of benign and malignant breast tumours. Contrast-enhanced MR images obtained 24 h or more after treatment demonstrated the laser-induced necrosis as a new area of non-enhancement, findings which correlated accurately with histological extent of tissue necrosis. The residual tumour after treatment of malignant tumours was accurately shown on MR when imaged 24 h after ILP in cases treated with a single fibre and 48 h in cases treated with multiple fibres. Real time MR imaging showed an evolving zone of signal loss, which at the end of ILP correlated closely with histological extent of laser induced necrosis.
This thesis has shown that MR imaging is a promising technique for the locoregional staging of breast cancer and for monitoring ILP therapy to breast tumours. However, many technical modifications are necessary before the results based on MR imaging can be used as the definitive guide in selecting surgical treatment or to confirm complete tumour ablation with percutaneous therapies. These issues and some potential solutions are discussed within this thesis.
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DEDICATION

To

my late father whom I miss so dearly,
my mother whom I love the most,
and my wife and children whom I adore the most.
ACKNOWLEDGEMENTS

The work for this thesis was carried out at the Department of Radiology and the National Medical Laser Centre, University College Hospitals, London and at Royal Surrey County Hospital, Guildford. My supervisors were Professor SG Bown and Mr T Davidson. I am greatly indebted to both for the support and encouragement they gave me throughout the project. I am particularly grateful to Dr MA Hall-Craggs who most definitely was the major driving force in the successful completion of my research period. My most sincere thanks are to Professor I Taylor who provided me the opportunity to begin this research, and was always willing to critically discuss my results. I am also grateful to Mr MW Kissin who has always supported the clinical studies undertaken in this thesis and was most willing in allowing his patients to participate. I would also like to acknowledge Mr P Boulos who first brought me to University College Hospital, and supported me throughout my research and clinical period.

Several people have contributed significant time and effort in allowing me to start and complete this research. Among these I am grateful to all our patients who willingly participated in these studies at their most difficult times, the pathologists (Dr A Wotherspoon, Dr G Cowley, Dr W Thurrell, Dr L Benjamin, Dr Cooke, Dr T Lewis) who helped in preparing the specimens for correlation with the MR images, and in the detailed interpretation of the histological slides necessary for the studies in this thesis. My thanks are also to Dr Giovanni Buonaccorsi and Dr Paul Ripley who despite other busy clinical commitments were able to assist in the laser treatments at rather short notices. The staff at the MR unit of Middlesex Hospital in particular Ms Maria Maloney deserve a special thanks for being very accommodative with all my requests.

There are several other people whose support I would like to acknowledge as each played an important role during my research period. They include the following: Lorraine Acheson, Amanda Jones, Sally Thorpe, Jane Stumcke, Helen Petterson, Doug Whitelaw, Dr K Walmsley, Professor M Hobsley, Ian Wilkinson, Martin Paley, Mr Ali, Abdulhamid, Marilene Loizidou, Kathy Fan, Dr Tony Leathem, Miriam Dwek, Abdul Gafour, Tariq Gauhar, Naeem Rehman.

I am also grateful to my brothers and sisters for their love and support during this period especially to Dr Faiz Mumtaz and his wife Dr Talat Mumtaz who in addition gave me the much needed financial support during this period.
STATEMENT OF ORIGINALITY

The work undertaken in this thesis involved guidance from Dr MA Hall-Craggs (Consultant Radiologist), Professor SG Bown (Professor of Laser Medicine and Surgery) and Mr T Davidson (Senior Lecturer and Consultant Breast Surgeon). All patients included in this study were recruited following ethical approval obtained at University College Hospital, London and Royal Surrey County Hospital, Guildford.

The clinical studies presented in this thesis were designed by myself. The concept of imaging ILP with MR imaging was based on the preliminary results of my predecessor Mr S Harries. All MR images were read initially by Dr MA Hall-Craggs and myself without knowledge of the histological findings. The MR images interpretation criteria were developed by Dr MA Hall-Craggs and myself. The mammograms were interpreted by Dr K Walmsley (Consultant Radiologist). The imaging-histopathological correlation's were done by myself in conjunction with designated breast pathologists (Dr A Wotherspoon, Dr G Cowley at University College Hospital and Dr T Lewis at Royal Surrey County Hospital, Guildford). All the data presented in this thesis were subsequently analysed by myself.

Clinical studies involving ILP of breast cancers and fibroadenomas were performed by myself and assisted in some cases by the staff in the department of Radiology, University College Hospitals, London. They included Dr Z Amin, Dr MA Hall-Craggs, Professor W Lees, and Dr J Brookes. The idea of treating fibroadenoma with ILP was thought of by myself and Professor SG Bown. The laser support during treatments was given by Dr G Buonaccorsi and Dr P Ripley.

The results of this thesis have contributed significantly to the interpretation and clinical indications for the use of contrast-enhanced breast MR imaging. Clinical studies of MR monitoring of ILP in breast tumours are all novel and have not been described by any other group.
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<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>C</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>CNB</td>
<td>Core needle biopsy</td>
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<td>CR</td>
<td>Complete response</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>2D</td>
<td>two-dimensional</td>
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<tr>
<td>3D</td>
<td>three-dimensional</td>
</tr>
<tr>
<td>DCIS</td>
<td>Ductal carcinoma <em>in situ</em></td>
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<tr>
<td>DNA</td>
<td>Deoxy ribonucleic acid</td>
</tr>
<tr>
<td>EIC</td>
<td>Extensive intraductal component</td>
</tr>
<tr>
<td>FA</td>
<td>Flip angle</td>
</tr>
<tr>
<td>FDG</td>
<td>Fluorine-18 labelled deoxyglucose</td>
</tr>
<tr>
<td>FLASH</td>
<td>Fast low angle shot</td>
</tr>
<tr>
<td>FNAC</td>
<td>Fine needle aspiration cytology</td>
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<tr>
<td>FOV</td>
<td>Field of view</td>
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<tr>
<td>G</td>
<td>Grade</td>
</tr>
<tr>
<td>Gd-DTPA</td>
<td>Gadolinium-diethylene triamine penta acetic acid</td>
</tr>
<tr>
<td>Gy</td>
<td>Gray</td>
</tr>
<tr>
<td>H&amp;E</td>
<td>Haematoxylin and Eosin</td>
</tr>
<tr>
<td>IDC</td>
<td>Invasive ductal carcinoma</td>
</tr>
<tr>
<td>ILC</td>
<td>Invasive lobular carcinoma</td>
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<tr>
<td>ILP</td>
<td>Interstitial laser photocoagulation</td>
</tr>
<tr>
<td>LCIS</td>
<td>Lobular carcinoma <em>in situ</em></td>
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<tr>
<td>J</td>
<td>Joules</td>
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<tr>
<td>MR</td>
<td>Magnetic resonance</td>
</tr>
<tr>
<td>NADP</td>
<td>nicotinamide adenine dinucleotide phosphate</td>
</tr>
<tr>
<td>Nd:YAG</td>
<td>Neodymium yttrium aluminium garnet</td>
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<tr>
<td>NSABP</td>
<td>National Surgical Adjuvant Breast and Bowel Project</td>
</tr>
<tr>
<td>MHz</td>
<td>Megahertz</td>
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<tr>
<td>NU</td>
<td>Normalised Units</td>
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<tr>
<td>PET</td>
<td>Positron emission tomography</td>
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<tr>
<td>RODEO</td>
<td>Rotating delivery of excitation of resonance</td>
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<tr>
<td>Abbreviation</td>
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<tr>
<td>ROI</td>
<td>Region of interest</td>
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<tr>
<td>SE</td>
<td>Spin echo</td>
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<td>STIR</td>
<td>Short tau inversion recovery</td>
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<td>T1W</td>
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<td>TE</td>
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<td>US</td>
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<td>WLE</td>
<td>wide local excision</td>
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OVERALL OBJECTIVE OF THESIS

(a) To investigate the accuracy of contrast-enhanced MR imaging compared with mammography in the locoregional staging of primary breast cancer, the diagnosis of local recurrence within the breast and assessment of residual disease after neoadjuvant therapy.

(b) To investigate the role of MR imaging in the guidance and monitoring of interstitial laser photocoagulation as a potentially minimally invasive treatment of benign and malignant breast tumours
SECTION A: BACKGROUND - REVIEW OF LITERATURE

CHAPTER 1: DIAGNOSIS OF BREAST CANCER

CHAPTER 2: BREAST MAGNETIC RESONANCE (MR) IMAGING

CHAPTER 3: BREAST CONSERVATION THERAPY

CHAPTER 4: INTERSTITIAL LASER PHOTOCOAGULATION
CHAPTER 1: DIAGNOSIS OF BREAST CANCER

1.1 CLINICAL EXAMINATION

1.2 TISSUE DIAGNOSIS
   1.2.1 Fine needle aspiration cytology
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1.3 IMAGING
   1.3.1 X-ray mammography
   1.3.2 Ultrasonography
   1.3.3 Computed Tomography
   1.3.4 Scintimammography
   1.3.5 Angiography
   1.3.6 Thermography

1.4 TRIPLE ASSESSMENT

1.5 SUMMARY
This chapter gives a summary of the methods available for the diagnosis of breast cancer. These methods include clinical examination, imaging and tissue diagnosis. Weak points of each method are emphasised to attract attention to those areas where additional information is desirable.

1.1 CLINICAL EXAMINATION

A breast lump is the most common clinical breast problem causing women to seek treatment and remains the most common presentation of breast cancer. Haagensen (1986) observed that 65% of 2198 breast cancer cases identified before the use of screening mammography presented as breast masses. Breast pain, a change in the size and shape of the breast, nipple discharge, and changes in the appearance of the skin are infrequent symptoms of carcinoma. Physical examination is easy to perform and of low cost. Mittra (1994) in the Lancet recommends physical examination without mammography for screening.

Clinical examination requires trained staff and is subject to significant interobserver variation. In addition, with the advent of mammographic screening, the percentage of symptomatic breast cancer in the developing countries is on the decline. Clinical measurements of tumour size have been shown to correlate rather poorly with pathological measurement (Fornage et al, 1987; Farouhi et al, 1994).

1.2 TISSUE DIAGNOSIS

The modern management of breast cancer requires a definitive tissue diagnosis of breast cancer to be made prior to discussion with the patient of the possible treatment options.

1.2.1 Fine needle aspiration cytology (FNAC)

The popularity of fine needle aspiration cytology (FNAC) has increased to the point that it currently forms a mandatory work up of all palpable breast lesions. For palpable breast masses, the technique offers several advantages: simplicity, good accuracy, low morbidity, minimal patient discomfort, relatively low cost, and immediate availability and reporting in a single outpatient visit.

A review of 31,340 FNACs in the medical literature indicates that the sensitivity and specificity of FNAC vary widely between reporting groups (Hermans, 1992). In that review, the reported sensitivity ranged from 65% to 98% and the specificity from 34% to 100%. The optimal results of FNAC depend upon three factors: histological type of the tumour, operator and interpreter's experience. Ciatto et al (1993a) analysed 9533 cases of FNAC, and showed an overall sensitivity of 89.5%. The sensitivity of FNAC was...
dependent upon the histological type of the tumour, with invasive lobular carcinomas and \textit{in situ} carcinoma having a lower sensitivity (84.5\% and 79.6\% respectively) compared to invasive ductal carcinoma (90.1\%).

Fine needle aspirates from breast tumours can give an indication of tumour type, grade (Ciatto et al, 1993b; Robinson et al, 1994), oestrogen and progesterone receptor status (Redard et al, 1989) and proliferative indices (Remvikos et al, 1991). In a study reported by Robinson et al (1994), histological grading of the excised tumour using Elston’s modified Bloom and Richardson method correlated accurately with preoperative cytological grading. The cytological features used for grading included cellular dissociation, cell size, uniformity, nucleoli, nuclear margin, and chromatin pattern. The results of this study suggest that cytological grading may substitute histological grading.

The limitations of FNAC include its inability to distinguish invasive from non-invasive carcinoma (Ballo and Sneige, 1996) as the latter tumour type requires the careful study of overall architecture and basement membrane integrity that only histopathology can provide. In addition as indicated earlier, the results of the technique are dependent upon the operator and interpreter’s experience.

1.2.2 Core needle biopsy (CNB)

Core needle biopsies (CNB) performed with a variety of devices has recently gained popularity in the evaluation of both palpable and non-palpable breast lesions. Physicians who favour this technique believe that the tissue samples obtained by CNB provide material for a more definitive diagnosis and can be interpreted by any pathologist without requiring the special skills of a cytopathologist.

Fentiman (1990) reviewed seven studies evaluating "Tru-Cut" needle biopsy for confirmation of malignancy in breast lumps. The sensitivity ranged from 74\% - 95\%, and the specificity from 96\% - 100\%. CNB appears to be superior than FNAC in the evaluation of nonpalpable lesions (Dowlatshahi et al, 1991). However, for the evaluation of palpable tumours, FNAC has been shown to have a higher sensitivity than CNB (97.5\% versus 90\%) (Ballo and Sneige, 1996). In the latter study, the addition of CNB to an already negative FNAC failed to increase sensitivity in the detection of carcinoma.

In addition to histological type, CNB can provide additional prognostic information including histological grade, steroid receptor status and proliferative indices. Baildam et al (1989) studied 140 patients who had "Tru-Cut" biopsies, and were able to accurately predict histological grade in 90\% of biopsies, steroid receptor status in 45\%, and were able to carry out DNA (de-oxy ribonucleic acid) flow cytometric studies in 30\% of biopsies.
Although core biopsy can help confirm invasion with accuracy it cannot reliably indicate the absence of tumour invasion when only ductal carcinoma *in situ* (DCIS) is found (Liberman et al, 1995a). The authors showed that the positive predictive value of core biopsy for the presence of invasion was 98%, but the negative predictive value was only 80%. Newer method of tissue acquisition that obtain larger core biopsy specimens and sample contiguously may decrease the likelihood of missing the invasive component of a cancer containing both DCIS and infiltrating ductal carcinoma (Parker et al, 1994).

To ensure specimen adequacy of CNB, a minimum of five cores (range, four - eight cores) is recommended to ensure adequacy by the CNB method (Liberman et al, 1994), however needle size is an important factor. In contrast, an average of four passes (range, three to six passes) are recommended for a successful FNAC (Ballo and Sneige, 1996) and this is associated with significantly less bruising compared with several core biopsies. Both techniques are associated with displacement of carcinomatous epithelium outside the tumour mass; the biological significance of this phenomenon however remains undetermined.

Sampling errors using core needle biopsy may even be greater compared to fine needle aspiration. This may be due to several factors; immobilisation of the lesion may be difficult, the possibility of a pneumothorax or of piercing beyond the mass often necessitates that the physician chooses a longer pathway for the needle than would normally be done with FNAC: core biopsy devices allow for one monodirectional sample of the lesion, whereas FNAC permits multidirectional passes though the mass, and finally core devices are associated with decreased tactile sensitivity compared with FNAC (i.e., firing a spring loaded device versus inserting a small needle).

Historically, CNB was thought to be more reliable than FNAC (Elston et al, 1978; Owen et al, 1980) but these reports were likely to have been influenced by the fact that FNAC was a new procedure at that time. The reliability of both techniques is dependent upon the ability and experience of the investigator. The exact decision to use either CNB or FNAC needs to be considered in the context of clinical presentation and whether the mass is palpable or not. In palpable lesions and in those in which imaging guidance is not justified, FNAC is the most cost-effective, and reliable procedure. In a stereotactic-guided biopsy setting, complimentary FNAC and core biopsy has been shown to provide maximum information and can avoid a repeat procedure (Sneige at al, 1996)

1.2.3 Excisional / Incisional biopsy

Excision breast biopsy is the complete removal of a lesion, with or without a rim of surrounding normal parenchyma. The excisional biopsy is usually the definitive treatment
of benign lesions. Excisional biopsy is also performed for clinically occult lesions detected and localised on imaging studies usually mammography. Incisional biopsy has largely become unnecessary with the availability of core needle biopsy techniques.

1.3 IMAGING

1.3.1 X-ray mammography

The first reported use of radiography for imaging the breast related to mastectomy specimens in 1913 by Albert Salomon, a surgeon. However it was not until 1930 that radiologist Stafford L. Warren described a stereoscopic method of in vivo mammography. The technique was subsequently popularised by Egan in 1960, who described a more dedicated approach to mammographic imaging using industrial film with a high milliampere-low kilovoltage technique, and reported 2 years later of 53 cases of clinically occult carcinoma detected in 2000 consecutive mammographic examinations (Gold, 1992).

In part inspired by Egan’s radiographic discovery of clinically occult breast cancers, a randomised screening trial involving approximately 62,000 women known as the Health Insurance Plan study of New York was undertaken in 1963 (Strax et al, 1973). The follow up results at 5 years demonstrated a mortality reduction of almost one thirds for women who underwent screening, a result that has remained significant through 19 years of subsequent evaluation. Further screening trials in Europe and elsewhere have shown similar survival benefits in cancers detected by mammographic screening (Anderson et al, 1988; Tabar et al, 1992). The use of mammography to screen asymptomatic women 50 years of age and over for early detection of breast cancer has been shown to reduce mortality rates by 20% to 30% (Fletcher et al, 1993), although debate continues on the optimal age at which to begin screening and the appropriate frequency of testing.

1.3.1.1 Symptomatic breast cancers

The value of mammography for screening is well established and is currently the only technique with proven efficacy for breast cancer screening. However, in the evaluation of women with signs or symptoms of breast cancer, the use of mammography as a diagnostic procedure is less efficacious (Kopans, 1992). Mammography is an excellent method for finding early stage cancers, but no absolute criteria distinguish malignant from benign lesions. This is further affected by the significant variability in the radiologists' interpretations of mammograms (Elmore et al, 1994). Radiologists with a high true-positive rate also tend to have a high false-positive rate in the diagnosis of breast cancer.
Fentiman (1990), in a review of 10 studies, showed the sensitivity of mammography varied from 61% - 87%. The sensitivity was lower in women less than 50 years of age (56%) compared to those over the age of 51 years (78%). Thus for patients in whom there is likely to be the greatest amount of clinical uncertainty the sensitivity of mammography is at its lowest for both exclusion and confirmation of malignancy. In a series of 306 women with invasive cancer, Joensuu et al (1994) showed that the frequency of normal mammogram was small (13%) among women aged over 50 years, but 35% among those aged 50 years or younger. The latter finding may in part be due to the increased incidence of radiodense breast in under 50 years old age group (Jackson et al, 1993). Furthermore women with normal mammogram had larger primary tumour size and more often positive axillary nodes (Joensuu et al, 1994). Mammography is not recommended in patients under 30 years of age (Williams et al, 1986). In a series of 76 patients, Williams et al (1986) showed that in 74% of cases referred for study of a palpable mass, no mass was evident on mammography and when a mass was seen, radiographic features did not influence subsequent management.

In the symptomatic patient, the mammogram serves to reinforce the diagnosis of cancer and helps to avoid overlooking a malignancy. If the clinical examination raises concern, a negative mammographic result should not delay further investigation. It is best to think of mammography as a screening study. The primary value of mammography in the symptomatic patient is to survey the remainder of the ipsilateral breast and to screen the contralateral breast to detect clinically occult cancer (Dixon and Chetty, 1991). Roubidoux et al (1995) retrospectively reviewed the records of 77 patients with suspected bilateral breast cancer. The contralateral cancer was detected at mammography in 88% of cases, and was a synchronous cancer in 43% of cases.

Of the invasive cancers, mammography is less accurate at diagnosing invasive lobular carcinoma (Hilleren et al, 1991). This may be due to the infiltrative pattern of invasive lobular carcinoma that usually does not destroy anatomical structures or excite a significant connective tissue reaction (Martinex and Azzopardi, 1979). In addition, invasive lobular carcinoma appears to be less associated with microcalcifications (Krecke and Gisviold, 1993).

Mammographic measurements of invasive tumour size has been shown in several studies to be inaccurate. The Yorkshire Breast Group (1980) showed a correlation between pathological and mammographic measurement in only 59% of cases. In a series of 200 palpable cancers, Pain et al (1992) reported that the tumour was not detected on the mammogram in 12 (6%) cases, was partially off the mammogram in 43 (21.5%) cases and was of indeterminate size in 36 (18.0%) cases, for reasons not stated. Overall accurate measurement was attained in only 72.5% of cases. In a recent study reported by Flanagan et al (1996), mammographic measurement had an almost 1:1 correlation with pathologic
size, however this series included patients in whom only a mass lesion was seen on mammography. Patients with normal or mammograms with microcalcifications only were excluded from analysis. Several studies have shown that the presence of mammographic microcalcifications and a normal mammogram are both associated with an increased risk of residual disease at reexcision (Macmillan et al, 1995; Walls et al, 1995). However these features do not guide in the extent of resection required to achieve complete tumour resection.

1.3.1.2 Non-invasive breast cancer

DCIS is uncommon in symptomatic patients, representing approximately 5% of breast cancers, but it is encountered increasingly in asymptomatic women because of the widespread use of mammographic screening, where 20% - 40% of clinically occult lesions are DCIS (Rebner and Raju, 1994). DCIS most often manifests as one or more cluster of irregular shaped microcalcifications (Stomper and Connolly, 1992). The calcification in DCIS are typically either branching, irregular, pleomorphic casts of ducts or more focal, irregular, granular type deposits. Studies have attempted to correlate pattern of microcalcification with histological type of DCIS. The authors also noted that comedo subtype was more likely to be associated with linear calcifications whereas noncomedo subtypes with granular calcifications. However, considerable overlap between the two subgroups exist and the authors concluded that one cannot accurately predict the histological subtype on the basis of mammographic appearances of the calcifications. Other authors (Holland and Hendricks, 1994) observed that DCIS without necrosis is commonly associated with a normal or an abnormal mammogram without calcifications. Based on the extent of microcalcifications, mammography usually underestimates the size of DCIS, although this discrepancy is less than 2 cm in 80% of cases if state of the art mammography is used (Holland and Hendricks et al, 1994).

Although DCIS most often manifests as calcifications, other less common manifestations have been reported. Ikeda and Andersson (1989) examined atypical forms of DCIS. In their series of 190 patients, 71 women did not have microcalcifications associated with DCIS. Of these, 30 had negative mammograms, 15 had circumscribed masses, and 12 had various nodular pattern. Seven of the 15 circumscribed masses represented intracystic papillary carcinoma, a subtype of DCIS. Other patients had asymmetry (n=1), dilated retroareolar ducts (n=2), focal architectural distortion (n=4), a subareolar mass (n=3), and a developing density (n=4).

Mammographic features are also unable to differentiate DCIS from invasive carcinoma. Hermann et al (1991) examined 193 consecutive women with nonpalpable breast carcinoma: 102 had DCIS, and 91 had infiltrating carcinoma. Of the 112 women (58%) with microcalcifications, 84 (75%) had DCIS and 28 (25%) had infiltrating carcinoma. Of
the 69 (36%) with a mass, 60 (87%) had infiltrating carcinoma. Of the 12 (6%) with microcalcifications and a mass, nine (75%) had infiltrating carcinoma. Thus, calcifications were more likely to be associated with DCIS. Masses, with or without calcifications, were more likely to represent infiltrating carcinoma. However, overlap existed between the two groups and the authors could not rely on the mammographic findings to distinguish DCIS from small infiltrating ductal carcinomas.

Lobular carcinoma in situ (LCIS) appears to be an incidental finding in a mammographically initiated biopsy, but has no direct mammographic correlates (Sonnenfeld et al, 1991). In the study of Sonnenfeld et al, 41 cases of LCIS were found. Thirty one (76%) of the cases had incidental benign microcalcifications as the mammographic abnormality that generated the biopsy. The majority of the calcifications that prompted the biopsy were found adjacent to the areas of LCIS and were associated with fibrocystic change. Rarely, when calcifications were directly correlated with LCIS, adjacent areas of benign tissue also had morphologically similar calcifications.

### 1.3.1.3 Diagnosis of local recurrence within the conserved breast

The role of mammography in the diagnosis of breast recurrences has been evaluated in numerous studies. The general agreement in these studies is that mammographic differentiation of recurrent cancer from benign changes attributable to surgical excision and radiation is usually difficult (Stomper et al, 1987; Hassell et al, 1990; Orel et al, 1992) due to overlap in their morphological appearances. Thus mammographic detection of local recurrence depends upon serial examination after breast conserving therapy to observe whether these changes stabilise or increase with follow up.

In most series, the percentage of local recurrences detected solely by mammography are similar to those detected solely by clinical examination, findings that suggest a complimentary role of the two modalities in the detection of local recurrence. In a series reported by Orel et al (1992), mammography had an overall sensitivity of 55% and overall positive predictive value of 72% compared with clinical examination that had a sensitivity of 66% and overall positive predictive value of 66% in the diagnosis of local recurrence. Clinical examination had a better sensitivity for recurrences within the lumpectomy site. However, recurrent tumours detected solely by mammography tend to be non-invasive and therefore of favourable prognosis (Orel et al, 1993).

### 1.3.1.4 Assessment of response to neoadjuvant chemotherapy

There are few reports in the literature that have evaluated the role of mammography in the assessment of response to neoadjuvant chemotherapy (Segel et al, 1988, Bonnadona et al, 1990; Moskovic et al, 1993, Vinnicombe et al, 1996; Helvie et al, 1996). Segel et al
(1988) reported on a series of 60 locally advanced breast cancers treated with neoadjuvant chemotherapy of which mammography identified 15 of the 17 patients with an excellent pathological response (i.e., minimal or no residual disease). The authors noted that microcalcifications may decrease in number following chemotherapy but rarely dissapeared and that their persistence did not necessarily indicate residual disease. Mammographic changes in the size and density of the spiculated mass appeared more reliable in showing response to chemotherapy. Bonnadona et al (1990) found complete response depicted at mammography in only six of the 27 patients who demonstrated complete response at clinical examination.

Moskovic et al (1993) observed complete response on mammography in 2 of the 22 patients with large operable tumours treated with neoadjuvant chemotherapy only. However, at pathological examination residual invasive disease was seen in all 22 patients. In a series of 95 patients reported by Vinnicombe et al (1996), complete mammographic response was seen in eight patients, of whom five had residual invasive disease on histological examination. In the same series, of the eight patients with a complete pathological response, only three had a complete mammographic response. These authors concluded that prediction of pathological outcome was not possible based on mammography. Helvie et al (1996) observed that although the sensitivity of clinical examination for prediction of residual carcinoma following neoadjuvant chemotherapy was only 49% compared with 79% for mammography, its specificity was higher 92% versus 77% for mammography.

In summary, while mammography may be useful in indicating response to chemotherapy, it is not accurate enough to avoid surgical treatment or guide in the extent of surgical resection required.

1.3.1.5 Advances in mammography

Advances in mammography are aimed to improve lesion detection and classification. Many experts agree that the next strides in mammography will occur with advances in digital technology (Shtern, 1992). Digital technology may provide several advantages over film/screen mammography, including a wider dynamic range which may allow wider variation in exposures such that subtle, inherent tissue contrast can be more easily seen, and these contrast differences can be amplified and exposure error minimised. In addition computed digital images can be transmitted for interpretation at distant sites.

Other methods currently being developed include computer aided diagnosis and the use of artificial neural networks (Chan et al, 1988; Nishikawa et al, 1993). These are aimed at improving the accuracy of lesion classification by the radiologist. The series reported by Nishikawa et al (1993) showed that artificial neural network based on human-extracted
features correctly classified all malignant cases (100% sensitivity), with a 41% false-positive results comparing favourably to radiologist, who achieved 89% sensitivity and 60% false positive results for the same cases.

In summary, despite the progress being made in X-ray mammography, detecting breast cancer in younger women with mammographically dense breasts or the surgically altered breast remains a challenge, as does determining which breast lesions require biopsy. In response to the diagnostic deficiencies of mammography, there have been investigations of a variety of other non-invasive modalities for the diagnosis of breast cancer.

1.3.2 ULTRASONOGRAPHY (US)

The most readily accepted use of ultrasonography has been to distinguish a simple cyst from a solid lesion. When all criteria for a simple cyst are strictly adhered to, the accuracy of ultrasound is 96% - 100% . However, cysts constitute only 25% of all palpable or mammographically detected lesions, which therefore leaves the remainder of breast lesions into the indeterminate or solid nodule categories (Hilton et al, 1986).

Several studies show a significant overlap in the ultrasonographic characteristics of benign and malignant tumours. Fentiman (1990) reviewed five studies evaluating ultrasound in the diagnosis of palpable breast tumours and showed an average sensitivity of 84% and a specificity of 89%. More recently, Stavros et al, 1995, re-evaluated the US characteristics of solid breast nodules and found a combination of three ultrasonographic features was associated with a very low risk of carcinoma: (a) an intensely hyperechoic mass, (b) an ellipsoid shape with a thin echogenic capsule, and (c) two or three gentle lobulations plus a thin echogenic capsule. In this series, only two of 424 prospectively classified masses with these features were malignant (0.5%). They stressed that by excluding any nodule with even a single finding of malignancy from the benign category, the sensitivity for cancer was 98.4%.

Ultrasonography is a valuable adjunct to clinical examination and mammography for determining the size and location of a lesion, especially in young women with dense breasts and women who have undergone augmentation mammoplasty. It is also useful in guiding cytologic aspiration (Jockich et al, 1992). Ultrasonography is useful for detecting enlarged axillary nodes but is unable to accurately differentiate benign from malignant nodes (Bruneton et al, 1986).

The quality and information content of ultrasonographic examination is highly dependent on the type of equipment used and the experience of the examiner. The results shown by the study by Stavros et al (1995) were based on state of the art real time ultrasonographic equipment plus an extensive sonographic examination which is usually not performed at
most breast imaging centres. The early detection of cancer or the detection of small clinically occult carcinomas is rarely possible with ultrasonography due to its limited spatial resolution and its insensitivity to microcalcifications. Malignant calcifications within DCIS and microscopically invasive ductal carcinoma, which do not have associated sonographically demonstrable masses are difficult to identify sonographically. Findings such tumours is the goal of mammographic screening, and ultrasound cannot compete with mammography in this arena, and therefore has no role in breast cancer screening.

The doppler effect of ultrasonography has been investigated to further improve specificity. High velocity flows seem to be only found in breast cancers (Cosgrove et al, 1993). In a series of 222 breast lesions (58 cancers) colour doppler ultrasound showed a sensitivity of 98% and a specificity of 89% for the diagnosis of breast cancer. The report concluded that “colour doppler signal in a lesion otherwise thought to be benign should prompt a biopsy, while the absence of signals in an indeterminate lesion is reassuring”. Because benign lesions may exhibit increased flow and more importantly, because a significant number of cancers (particularly those less than 1 cm in diameter) do not exhibit evidence of abnormal flow, Doppler ultrasound is not yet reliable for distinguishing benign from malignant lesions.

### 1.3.3 COMPUTED TOMOGRAPHY (CT)

The increased uptake of radioactive iodine by breast carcinomas was described by Eskin and co-workers in 1974. Using the criterion of lesion enhancement with intravenous injection of iodinated contrast agents, Chang et al (1978) found CT to be more sensitive than mammography (94% versus 77%) in the diagnosis of breast cancer and emphasised the improved sensitivity in radiodense breasts. However the enthusiasm in CT of the breast was not sustained. In the series reported by Muller et al (1983), malignant tumours did not show significant contrast-enhancement and CT did not provide any additional information not shown on mammography. In addition, the radiation hazard was shown to be three to six times that of diagnostic X-ray mammography (Muller et al, 1983).

With recent improvements in CT technology, images with high spatial and contrast resolution have been shown to be produced with potentially lower radiation exposure. In a recent study (Hagay et al, 1996), contrast-enhanced CT proved to be of value in the diagnosis of local recurrence following breast conservation therapy. The sensitivity was 91% with a specificity of 85% for the diagnosis of local recurrence within the conserved breast.

Despite these encouraging results, computed breast tomography has not come into routine clinical use mainly due to the radiation hazard to both breasts and thorax, and the
relatively large dose of contrast medium (300 ml of 30% diatrizoate dimeglumine solution) required. In addition, the exact clinical benefits of CT compared to mammography have not been adequately addressed.

1.3.4 SCINTIMAMMOGRAPHY

Several standard radiolabels (single photon emitters) have been investigated for their role in breast imaging. Piccolo et al (1994) evaluated Technetium-99m-methylene diphosphonate, an isotope used for routine bone scanning to image primary breast cancer. In a series of 200 patients (172 cancers), the sensitivity was 92% and specificity of 95% for the diagnosis of breast cancer. Other Technetium and Thallium based radio-isotopes that have been evaluated in breast cancer diagnosis have shown similar levels of high sensitivity (Mansi et al, 1996; Cimitan et al, 1996).

The sensitivity of scintimammography appears to be lower in non palpable cancers compared to palpable tumours greater than 1cm (Piccolo et al, 1994; Palmedo et al, 1996). Scintimammographic techniques have primarily focused on the differentiation of benign from malignant tumours. In most studies, no attempt has been made to correlate tumour size, detection of multifocal or multicentric tumours and DCIS with pathological findings.

Recent studies have compared scintimammography with X-ray mammography and magnetic resonance (MR) imaging in the diagnosis of primary breast cancer (Palmedo et al, 1996; Helbich et al, 1997). The series reported by Palmedo et al (1996) showed scintimammography using Technetium-99m-MIBI to have a higher specificity (62%, 75%) than X-ray mammography (15%, 25%) and MR imaging (15%, 50%) for the diagnosis of breast cancer in both palpable and non-palpable tumours. However, MR imaging had a higher sensitivity (100%) than both scintimammography (60%) and X-ray mammography (60%) in the evaluation of non palpable tumours. In the series reported by Helbich et al (1997) using Technetium-99m sestamibi, 75 breast lesions were evaluated. Planar imaging had a sensitivity and specificity of 62% & 88% respectively. The sensitivity improved to 83% with single photon emission tomography. In the same study, MR imaging had a sensitivity and specificity of 96% and 82% respectively for the diagnosis of breast cancer.

Scintimammographic techniques have been used to evaluate the axilla. Mansi et al (1996) showed a sensitivity of 91.6%, and a specificity of 92.3% in the diagnosis of axillary nodal metastases using Technetium-99m tetrafosmin. Avril et al (1996) using positron emission tomography (PET) imaging with [fluorine-18] 2-deoxy-2-fluoro-D-glucose (FDG) showed a sensitivity of 79%, and specificity of 96% in showing axillary node metastases in tumours greater than 2cm in size, but the sensitivity was only 33% in
tumours less than 2cm. Thus in clinical practice, PET cannot substitute for histopathological analysis in detecting axillary nodes metastases. Using Thallium-201, Cimitan et al (1996) showed a sensitivity of only 27% in the diagnosis of involved axillary nodes.

In one study, prospective evaluation of PET during breast cancer chemotherapy showed that the tumour FDG uptake declined rapidly and significantly, just 8 days after treatment was initiated. Further declines in FDG uptake were apparent at 21, 42, and 63 days of treatment in the patients who went on to complete or partial responses assessed 6 months later, whereas no significant decline in FDG uptake was seen in the non-responding patients (Wahl et al, 1993). Although, the results of this preliminary findings indicate that tumour metabolic changes precede changes in tumour size, the clinico-pathological correlate of such findings remain undetermined.

Bassa et al (1996) retrospectively evaluated the value of FDG-PET studies in 16 patients with locally advanced breast cancer treated with preoperative chemotherapy. The sensitivity for detection of residual disease post chemotherapy using FDG-PET studies, mammography and US was 75%, 71.4%, and 87.5% respectively. Similar assessment for residual nodal involvement was 41.6%, 71.4%, and 66.6% using the three imaging modalities. The standard uptake value of the FDG decreased in tumours that responded to chemotherapy.

A major disadvantage of PET imaging is the relatively high cost of PET scanners and the limited availability and short half life of cyclotron-produced radiopharmaceuticals. In addition, the size and volume of the primary tumour affects PET imaging (tumours less than 1cm in diameter frequently escape detection). Scintimammographic techniques involve exposure to radiation and have a long examination time (typically 60 minutes).

In summary, several metabolic and physiologic imaging methods that use nuclear medicine techniques are showing promise in breast cancer imaging. Before widespread clinical application can be expected, the precise role of these techniques will need to be defined through controlled prospective trials comparing metabolic imaging with other, more standard methods or with biopsy data and ultimately with patient outcome.

1.3.5 ANGIOGRAPHY

Few studies have been published on the value of angiography in the diagnosis of breast tumours. Watt et al (1986) examined 22 lesions by digital subtraction angiography with subsequent histopathological analyses and correctly diagnosed eight of nine cancers and 11 of thirteen benign lesions. Carcinomas exhibited a rapid initial blush in an area with an abnormal vascular structure for 30 s after the injection of a 30ml bolus of iodinated
contrast medium (5F pigtail catheter in the superior venacava). The opacification then faded and remained at a plateau for several minutes.

However, angiography is an invasive technique requiring contrast injection and necessitate relatively long examination time. The technique has not gained any popularity in clinical practice.

1.3.6 THERMOGRAPHY

There have been many reports on the value of thermography in the diagnosis of breast cancer. The high false negative rate (approximately 50%) in the series reported by Dodd (1977) and the inability to accurately localise the lesion for subsequent biopsy has made the technique not useful in breast cancer diagnosis. Van Dam et al (1988) evaluated 201 breast lesions and concluded that thermography was neither necessary nor helpful in the diagnosis. The thermographic criteria of malignancy are rarely produced by early carcinomas.

1.4 TRIPLE ASSESSMENT

Triple diagnosis refers to the application of three evaluation steps to a breast mass: clinical assessment by palpation, results of X-ray mammography, and results of FNAC. Triple assessment serves to overcome the limitations of each modality of breast examination. Layfield et al (1989) in an extensive review showed that the predictive value for benign disease when all three diagnostic tests are benign is 99%. The concept of triple assessment is further broadened such that a negative diagnostic test can be replaced by a suitable adjunctive test. For instance, a negative FNAC in the presence of a palpable mass can be evaluated by core needle biopsy. Furthermore, a negative mammographic examination in the presence of a clinical or cytologic suspicion needs to be evaluated by a suitable adjunctive imaging technique.

1.5 SUMMARY

Patients with suspected breast cancer need to be carefully evaluated in order to plan subsequent treatment appropriately. A tissue diagnosis is a mandatory initial investigation in the management of breast diseases. This can be reliably achieved with fine needle aspiration cytology. Core needle biopsy techniques are becoming popular and should be used in equivocal cases.

X-ray mammography is currently the "gold standard" imaging technique for diagnostic breast imaging. Currently no other imaging technique surpasses the role of X-ray mammography in screening for breast cancer. The limitations of the technique remain in
the detection of breast cancer particularly in younger women with radiodense breasts. In addition, its role in the differentiation of benign from malignant tumours and loco-regional staging of breast cancer in symptomatic patients appears limited. These deficiencies have stimulated research into alternative imaging techniques parallel with further advances in the field of X-ray mammography. Breast CT, angiography and thermography have not gained clinical popularity. Recent advances in ultrasonography and scintimammography appear promising and may have a role in the evaluation of breast tumours.

Of the alternative breast imaging techniques currently being evaluated, magnetic resonance (MR) imaging has received greatest attention. The present status of MR imaging of the breast is discussed in detail in the next chapter.
CHAPTER 2: BREAST MAGNETIC RESONANCE IMAGING

INTRODUCTION

2.1 HISTORICAL BACKGROUND

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INTRODUCTION

From early on in the development of magnetic resonance (MR) as a clinical imaging tool, it was realised that the high intrinsic soft tissue contrast and good spatial resolution gave MR the potential role in the evaluation of breast diseases. The use of intravenous contrast agents and the technological hard- and software improvements have further enhanced this potential in recent years. This chapter reviews the historical background in the development of breast MR imaging, the imaging techniques used and results of studies published that forms in part the basis for further research discussed in this thesis.

2.1 HISTORICAL BACKGROUND

Interest in the application of magnetic resonance imaging to the diagnosis of cancer dates back to the early 1970s when Damadian (1971) suggested that in vitro measurements of relaxation times might be useful in the diagnosis of cancer. He reported that in vitro T1 and T2 relaxation times were longer in cancers than in normal tissues. Studies on in vitro MR spectroscopy appeared soon after Damadian’s publication and showed that while the T1 and T2 relaxation times of malignant breast tissue were prolonged, overlap existed with benign breast tissue (Medina et al, 1975; Mansfield et al, 1979).

Once clinical MR imaging systems were developed, early clinical trials showed that MR imaging may have a role in breast cancer diagnosis (El Yousef and Duchesneau, 1984). During this period specialised radiofrequency breast coils were developed which improved image contrast on unenhanced MR scans (Stelling et al, 1985). However, detailed clinical studies revealed that MR imaging had little to offer compared with less expensive and more widely available conventional imaging methods (Turner et al, 1988).

Interest in MR imaging of the breast was re-stimulated with the introduction of gadolinium-chelate contrast agents for use with clinical MR imaging. Heywang et al. (1986), using a single breast coil and spin echo (SE) sequences operating at 0.35 tesla studied 20 patients who all subsequently underwent biopsies. All carcinomas enhanced on T1-weighted (T1W) SE images acquired after the injection of 0.2mmol/kg body weight gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA), suggesting that contrast-enhanced MR imaging was a highly sensitive test for primary breast cancer. Since 1986, further advances in MR imaging of the breast have focused on improvements in both hardware and software required for MR imaging.

2.2 TERMINOLOGY

The terminology used for MR imaging of the breast has varied in the literature and has included Magnetic Resonance Mammography, MR imaging of the breast and Breast MR
imaging. Weinreb and associates (1994) have cautioned against the use of the terminology "Magnetic Resonance Mammography". They have expressed concern that such a terminology may be deceptive by being suggestive to some that an MR imaging study of the breast is a replacement for or is superior to conventional X-ray mammography for breast cancer detection and have suggested that the term "Breast MR" imaging or "MR imaging of the breast" should be used.

2.3 CONTRAST MEDIA IN BREAST MR IMAGING

Complexes of the element gadolinium are the most widely used of currently available MR contrast agents. The gadolinium (Gd$^{3+}$) ion, with its spin quantum number of 7/2 and its long electron spin relaxation time, is particularly suitable for producing paramagnetic contrast enhancement (Gadian et al, 1985). The Gd$^{3+}$ ion is complexed with a chelating agent (such as diethylene triamine pentacetic acid [DTPA]) to reduce the toxicity of the free ion, and improve its osmolarity and water solubility allowing for more rapid renal elimination (Weinmann et al, 1984). The Gd$^{3+}$ bonds with three of DTPA's carboxyl groups, forming a -2 charged complex known as gadopentate. In its formulation as Magnevist, each mole of the (gadopentate)$^{-2}$ moiety is ionically balanced with two moles of (meglumine)$^{+1}$, resulting in the compound gadopentate dimeglumine. The volume of contrast agent used is 1/10 the volume of iodinated contrast medium ordinarily used in diagnostic radiography. The reported side effects include nausea or vomiting and short term reversible increase in serum bilirubin levels. Moderately severe anaphylactoid reaction is reported to occur in 1 in 5000 patients receiving Gd-DTPA (Niendorf et al, 1991).

The degree of paramagnetic contrast enhancement depends on the T1 and T2 values of tissues; the longer the tissue-specific relaxation times, the stronger the reduction effect of the contrast medium (Gadian et al, 1985). The net effect of the contrast medium is determined by the T1/T2 dependence of the given pulse sequence for the tissue in question. At low concentrations of Gd-DTPA, signal enhancement based on the shortening of T1 predominates; at high concentrations, a decrease in signal intensity based on the T2 effect predominates. Thus T1-weighted pulse sequences are particularly suited to detecting signal enhancement for the concentration of Gd-DTPA used in vivo.

When a bolus injection of a gadolinium chelate is given, the agent is transported through the heart and lungs. Although dilution occurs in the heart and lungs, the contrast agent enters the arterial system as a bolus. During the first-pass phase of the contrast agent the difference in concentration between intra- and extra-vascular compartments is at its maximum, and in this phase, transportation from the vessels into the tissues occurs rapidly. Contrast medium, present in capillaries and the extracellular extravascular space, provides enhancement (Strich et al, 1985).
The basic mechanism behind contrast-enhancement in MR imaging is thought to be differences between the vascularity of various tumours and normal breast parenchyma. Enhancement of breast cancers with iodinated intravenous contrast agents was first described by Eskin and co-workers in 1974 (Eskin et al, 1974). Neo-angiogenesis is a recognised feature of malignant breast tumours (Weidner et al, 1991). Angiographic studies of malignant breast tumours have demonstrated neovascularity, venous laking, early venous drainage (arteriovenous shunting), and perivascular cuffing (Watt et al, 1986). Although angiogenesis is a critical feature in the growth of malignant tumours, it is not unique to the latter, as “angiogenic” benign tumours exist. Benign inflammatory changes are also associated with hypervascularity. The latter findings may explain the basis of contrast-enhancement in some benign breast conditions.

Studies have correlated contrast-enhancement on MR imaging with tumour vascularity (Frouge et al, 1994; Hulka et al, 1995, Buadu et al, 1996). In all studies, a close correlation has been demonstrated between the rate of contrast-enhancement and microvessel density. In an animal tumour model (MCF7 human breast cancer implanted in nude mice), Furman-Haran et al (1996) showed the presence of dense permeable microcapillaries in the tumour periphery and in intratumoural regions that surrounded necrotic areas, findings which correlated with the pattern of contrast-enhancement on T2-weighted (T2W) SE images.

The onset and rate of contrast-enhancement in a given tissue depends on a complexity of factors which would include the number of vessels, the blood flow rate, the vascular resistance, the vessel wall permeability (due to abnormal basement membranes or to an effect of cytokines that promoting vessel growth), the composition of the extracellular space, and finally the venous outflow. These factors differ from tissue to tissue and consequently so will the enhancement curves (discussed in the next section).

The pulse sequence used in contrast-enhanced MR imaging may influence the dosage of intravenous Gd-DTPA. Kaiser and Zeitler (1989) used a dose of 0.2mmol/kg Gd-DTPA when using the spin echo sequence. However this resulted in "overinjection" of the breast parenchyma with gradient echo sequence and these authors recomend a dose of 0.1mmol/kg Gd-DTPA. In a further study using a gradient echo sequence, Heywang et al (1994a) showed that the diagnostic accuracy was better with a dosage of 0.16mmol/kg as compared to 0.1mmol/kg body weight. The higher dosage enabled visualisation of an additional three cancers (all smaller than slice thickness). However, it is not known whether these findings can be applied to other pulse sequences and imaging parameters.
2.4 IMAGING TECHNIQUES IN BREAST MR

There is no single standardised and generally accepted technique for all breast MR imaging examination. Different protocols have been favoured by different investigators based on available hardware and software, clinical indications, desired results, and personal preferences. The discussion below reviews the techniques currently used for breast MR imaging and their clinical results.

2.4.1 Dynamic contrast-enhanced imaging

During dynamic MR imaging, the temporal pattern of signal enhancement in the first 1 to 2 minutes is studied with the aim of differentiating malignant tumours from benign changes. Sections are acquired through the tumour before and at short intervals (typically 1 minute or less) immediately after contrast-material injection using identical imaging parameters. The enhancement process in region(s) of interest (ROI) is displayed as a time-signal intensity curve. The features of enhancement curves are described as follows:-

- **onset of enhancement**, this is the moment a structure starts to increase in signal intensity. The onset of enhancement of a given tissue can be related to enhancement of a nearby artery, which avoids variation due to difference in circulation time.
- **maximum slope of enhancement**, is the maximum enhancement rate during the first pass of the contrast material.
- **the plateau-phase** usually starts after several minutes, when enhancement of the specific tissue is maximal and an equilibrium has been reached.
- **the wash-out phase**, this is when the signal intensity declines due to contrast agent leaving the tissues and returning to the venous system for renal excretion.

Dynamic MR imaging was first reported by Kaiser and Zeitler (1989). The underlying hypothesis was that the differences in enhancement between malignant and other tissues is most conspicuous in the early-dynamic phase (i.e., first-pass phase). In a series of 25 patients examined by two-dimensional (2D) fast low angle shot (FLASH) sequence using a contrast dose of 0.1mmol/kg body weight, all six histologically proven cancers showed enhancement characterised by a sudden increase in signal intensity of the order of 100% compared with unenhanced images within the first two minutes after contrast-material injection. The authors found no overlap in the rate and peak of enhancement of benign and malignant tumours in the first two minutes of dynamic imaging, whereas after more than 10 minutes an overlap in the signal intensity was observed. These results were confirmed in a further study of 18 patients (9 carcinomas, 8 benign [mainly fibrocystic] lesions) by Stack et al (1990). In this study, using an arbitrary cut off point of 4 minutes and defining cumulative enhancement as 100%, the average time to achieve 90% of
cumulative enhancement was 60 s for malignant disease and 105 s for benign disease.

In a larger series reported by Kaiser (1994) using the above criterion of rate of enhancement, the author showed a sensitivity of 98.1%, and a specificity of 97.4% (n = 203 cancers of 2053 breast MR examinations) for the diagnosis of breast cancer. There were 47 false positive cases and 4 false negatives. To improve the specificity Kaiser (Kaiser, 1994) suggested that the washout phase of the enhancement curve should also be analysed. All carcinomas showed a constant or decreasing signal intensity after 2 minutes. The more rapid the washout phase, the higher the probability that the lesion is malignant. The rapid washout of contrast-material in malignant tumours may be related to the increased density of arteriovenous shunts induced by tumour angiogenesis.

However, dynamic MR imaging studies performed by other workers observed significant overlap in the time intensity curves of benign and malignant tumours which did not allow an improved diagnostic specificity of MR imaging (Flickinger et al, 1993; Orel et al, 1994a; Gilles et al, 1994a; Kerslake et al 1995; Stomper et al 1995; Bone et al, 1996). The criteria used for differentiating benign form malignant tumours and quantification of signal intensity have however differed in all these studies. The sensitivity in these studies ranged from 88% - 100% and the specificity 53% - 66% for the diagnosis of breast cancer.

To improve the diagnostic specificity further, other workers have suggested the use faster image acquisition during the first-pass phase, at least 1 image every two seconds (Boetes et al, 1994; Hulka et al, 1995; Chenevert et al, 1995). Boetes et al (1994) used a turboFLASH sequence with breast images acquired of a single selected section of the tumour every 2.3 seconds interval for 2 minutes after contrast-material injection. In this study, 11.5 seconds was used empirically as the cut-off point after aortic enhancement to distinguish benign and malignant tumours. This criterion yielded a sensitivity of 95% and a specificity of 88% for the diagnosis of breast cancer. There were 3 false negative cancers which showed no contrast-enhancement (2mm DCIS and 40mm invasive lobular carcinoma) or late enhancement (10mm DCIS). The false positive findings included chronic active periductal mastitis, lobular adenosis and epithelial hyperplasia. In another study (Boetes et al, 1995) observed the rate of enhancement in invasive ductal cancers to be greater than that of DCIS and invasive lobular cancers.

In a study of 13 patients, by using a temporal resolution of 12 s intervals, Chenevert et al (1995) detected one slowly enhancing cancer. Hulka et al (1995) study, using echo planar imaging with a temporal resolution of 6 seconds showed that even though cancers tended to enhance more rapidly, some overlap was detected between benign and malignant tumours. Slowly enhancing cancers and non-enhancing invasive and in-situ cancers have been described in the literature (Heywang-Koebrunner and Viehweg, 1994).
The pattern of contrast-material enhancement has been used by some workers to improve the specificity of dynamic imaging (Kaiser, 1994; Boetes et al, 1994). The authors found that fibroadenomas usually demonstrate initial peak enhancement in the centre of the tumour (centrifugal enhancement), whereas carcinomas tend to enhance most at the periphery (centripetal enhancement).

The data obtained during dynamic MR imaging of the breast has been used to provide prognostic as well as therapeutic information. Stomper et al (1995) attempted to correlate time-intensity curve parameters with pathological size, nodal status and hormone receptor status of invasive carcinomas, but found no significant correlation. In a latter study, an association between invasive carcinomas with a high DNA S-phase percentage (a measure of increased cell proliferation) and peripheral MR imaging enhancement pattern was observed; four of 6 lesions with peripheral enhancement had a high DNA S-phase percentage compared with 0 of 11 homogenous enhancing carcinomas which had lower DNA S-phase percentage (mean cut-off value of DNA S-phase in the study was 6.9%). However, there was no significant association between a high DNA S-phase percentage and greater contrast-enhancement amplitude, rate or washout (Stomper et al, 1996).

Tumour angiogenesis is an independent and statistically significant prognostic marker in breast cancer (Weidner et al 1992). As discussed earlier, the close correlation shown by several workers between the density and distribution of microvessels in malignant tumours and the rate of contrast-enhancement on dynamic MR imaging indicate its potential role as a non-invasive assessment of neoangiogenesis. Dynamic MR imaging has also been shown to be of value in monitoring response to neoadjuvant chemotherapy (Gilles et al 1994b; Knopp et al, 1994)

Limitations of dynamic imaging

Numerous approaches as shown in the discussion above have been proposed to quantify time-signal intensity changes in dynamic MR imaging but none appear ideal. Region of interest (ROI) analysis is prone to numerous errors, most obviously the subjective choice of region shape, size, position and patient movement. Tumours exhibit highly complex and heterogeneous patterns of enhancement in the majority of lesions and the variability of enhancement within any single tumour cannot be adequately quantified even when measurements are obtained from multiple ROIs. Thus when ROI analysis is used, the specificity of MR imaging is likely to remain inadequate even when dynamic studies of high temporal resolution are employed. Synthetic calculated images in which each pixel is individually quantified with respect to time course changes in signal intensity would allow tissue heterogeneity to be taken into account and would reduce subjectivity (Hoffmann et al, 1995). However, such an approach is very time consuming.
Not all MR scanners can run rapid sequences with sufficient slices to cover the entire breast. In these situations, dynamic imaging requires the preselection of the tumour site in which the kinetics of the contrast-material can be followed. This is usually selected on the unenhanced T1W images in which malignant tumours are usually of low signal intensity, and hence difficult to delineate if not surrounded by high signal fatty tissue. In addition, there is overlap in the appearance of benign and malignant tumours on unenhanced T1W images. This results in an inadequate dynamic study if the section chosen does not pass through the main tumour, consequently tumours are missed and contribute to false negative studies. In dynamic imaging studies, tumours not visualised on the pre-contrast images have been localised by placing vitamin E or cod liver capsules over the palpable abnormality or in cases of non-palpable abnormality, the mammographic location is used as a guide (Weinreb and Newstead, 1995). This reduces accuracy and the diagnostic potential of the study.

Because of the non-uniform pattern of enhancement of most breast tumours, it is desirable to sample the entire lesion. Ideally higher resolution three-dimensional (3D) dynamic contrast-enhanced MR would be more accurate in the assessment of pattern and rate of contrast-enhancement. (Chenevert et al, 1995). In older scanners without high performance gradients, there is significant trade off between spatial and temporal resolution, and the use of thicker slices may lead to small lesions and multifocal disease being missed.

Finally, if inherent biological differences (particularly microvessel density) are responsible for the observed differences in the enhancement rates of benign and malignant lesions and within malignant tumours, it is doubtful that faster acquisition techniques will achieve any substantial improvement in specificity (Baudu et al, 1996). Well vascularised tumours may enhance slowly under certain conditions, such as prolonged delivery of contrast-material, poor cardiac output, and obstruction of blood flow to the tumour owing to patient positioning. Therefore, the rate of enhancement alone (if not standardised), may be inadequate as a stand-alone interpretative criterion on contrast-enhanced MR imaging.

2.4.2 Static contrast-enhanced MR imaging

Some researchers have concluded that contrast-enhancement curves do not provide sufficient specificity to be of use in characterising tumours, and they have sacrificed temporal resolution and the dynamic information needed to generate time-intensity curves and instituted relatively slow (on the order of 2 - 5 minutes) scanning techniques that emphasise spatial resolution to optimise morphological detail and detection of small tumours (Heywang et al, 1989; Harms et al, 1993; Orel et al, 1995).
In static contrast-enhanced MR imaging, signal enhancement is evaluated by comparison of unenhanced and contrast-enhanced images. This can be done subjectively or quantitatively (e.g. enhancement index or ratio). The optimal time interval in which to observe a differential uptake of contrast agent between benign and malignant breast lesions is approximately 2 - 5 minutes following contrast injection. Beyond that time the signal intensity of normal breast tissue, which enhances more slowly, begins to approach that of malignancies (Kaiser and Zeitler, 1989; Heywang et al, 1989). Within the first 5 minutes it is possible to obtain high resolution data across the entire breast using a 3D gradient echo (GE) technique.

Heywang et al (1989) used the term normalised ratio for the quantitative evaluation of increase in signal intensity. This system of measurement uses a factor that sets fat adjacent to the lesion at 1500 NU (normalised units). The threshold for significant enhancement was found to be 250 NU for SE sequence (Heywang et al, 1989) and 500 NU for GE sequence (Heywang-Koebrunner and Viehweg, 1994). The authors currently use a 3D fast gradient echo sequence (FLASH) with an imaging time of 174 seconds without dynamic imaging and have demonstrated a sensitivity of 99.5% in the diagnosis of breast cancer.

Harms et al (1993) defined a positive finding to be of signal intensity higher than that of breast parenchyma irrespective of its morphological appearance on contrast-enhanced RODEO (rotating delivery of excitation of resonance) MR images obtained with an acquisition time of 5 minutes. Using this technique, these authors achieved a sensitivity 100% but a specificity of 59% for the diagnosis of breast cancer. The improved sensitivity enabled identification of an additional 11 clinically and mammographically occult cancers.

To improve the specificity of static contrast-enhanced MR imaging, Orel et al (1994a) have suggested the use of morphological criteria (border characteristics, internal architecture, enhancement characteristics) to aid lesion detection. A pattern of rim enhancement has been noted in cancers but not in benign tumours by several investigators (Orel et al, 1994a, 1995; Kerslake et al 1995; Stomper et al, 1995). Malignant lesions usually show heterogeneous enhancement with irregular or spiculated borders. Fibroadenomas may have regular, lobulated borders, and internal septation with “cluster of grapes” appearance. Such features were seen in 5 of 9 fibroadenomas but in no carcinomas in a series reported by Orel et al (1994a). However, some overlap in morphological characteristic is also known to occur, and cancers with well defined regular borders have been reported (Orel et al, 1995).
2.4.3 Fat suppression techniques

With the abundance of fat in the breast and its anatomic distribution, it is likely to appear in any chosen imaging plane. Fat produces a high signal on T1-weighted images and therefore determines the signal range represented by the gray scale. The absence of hyperintense fat signal can improve the ability to detect the T1-shortening effect of gadolinium based contrast agents. There are a number of different types of fat-suppression techniques, but not all are suitable for contrast-enhanced MR imaging. The most promising fat-suppression technique appears to the RODEO technique developed by Harms et al (1993). This allows rapid scanning (5 minutes) with excellent fat suppression, lack of susceptibility to magnetic field inhomogeneities, and a three dimensional acquisition capability. This technique requires a transmit-receive breast coil to reduce the power requirements and to limit the excited volume to a single breast. The RODEO technique is currently not available commercially.

Although fat suppression may have important benefits, it may also entail problems on some systems, and is not considered an absolute requirement for all breast-imaging studies. The technique is sensitive to patient motion, and any movement during a fat suppression sequence renders the entire study worthless. An alternative to fat suppression for increasing the conspicuousness of enhancing tumours is the use of subtraction techniques.

2.4.4 Subtraction imaging

Subtraction techniques are used to increase the conspicuousness of enhancing tumours. Subtraction of images acquired using the same parameters before and after contrast agent is administered, yields an image in which the difference in signal is directly proportional to the degree of contrast-enhancement. Fat will not enhance and is therefore effectively suppressed in the subtracted image.

Flanagan et al (1995) performed digital subtraction on selected images obtained using the 3D FLASH sequence. In a series of 31 patients, digital subtraction improved the accuracy of diagnosis in six patients compared with information displayed on the post-contrast 3D FLASH images. Subtracted images allowed better delineation of small sized tumours, tumour margins and multicentricity. However, motion artefact was seen in two patients and resulted in blurring which was particularly evident at the tumour margins. In the series reported by Gilles et al (1994a), respiratory and cardiac movements diminished the quality of subtracted images in 39 of 143 cases, however it did not appear to impair visualisation of contrast-enhancement.

Digital subtraction is a simple, cheap, post-processing technique that requires no extra
equipment and adds no extra time to patient examination. The technique has the advantage of being easy to implement regardless of magnetic field strength or hardware, and is not subject to the non-uniform fat suppression that affects some frequency selective techniques. Furthermore, it can be used in conjunction with almost any pulse sequence so that the desired temporal resolution is not compromised by fat suppression.

The disadvantage of the subtraction imaging is its sensitivity to patient motion and image misregistration. Image misregistration can result in spurious high signal on subtraction images. By using mild compression to stabilise the breast, failures resulting from misregistration can be limited. Motion artefacts are usually seen as recognisable patterns on the subtracted images, and are easily identified by review of the source images. The subtracted data has reduced signal-to-noise ratio and lacks the anatomic information present on the pre-subtracted images. By combining the unenhanced and contrast-enhanced images to produce a colour map of contrast-enhancement superimposed on a standard gray scale image, the latter limitation of subtracted images can be overcome. Contrast-enhanced lesions seen on subtracted images require confirmation and their morphology assessed on the unenhanced and contrast-enhanced source images.

2.5 CLINICAL RESULTS

2.5.1 PRIMARY BREAST CANCER

Diagnosis of breast cancer

The sensitivity of MR imaging in various studies for detecting carcinoma of the breast has varied from 80 - 100% (Heywang et al, 1989; Harms et al, 1993; Kaiser, 1994; Boetes et al, 1995; Fobben et al, 1995). In all these studies, the sensitivity of MR imaging for the diagnosis of breast cancer was greater than X-ray mammography and ultrasonography. In a series of 61 patients with breast cancer reported by Boetes et al (1995), MR imaging missed only 2% of the index tumours as compared with mammography which missed 10% and ultrasonography 15% of cases. However, Fobben et al (1995) reported that the sensitivity and specificity of MR imaging in the diagnosis of breast cancer with commercially available techniques (3D gradient echo sequence) was not significantly greater than mammography. In this study 91 breast abnormalities were evaluated, of which 21 were malignant. The sensitivity and specificity of MR imaging was 83% compared with mammography that had a sensitivity and specificity of 75% and 79% respectively for the diagnosis of breast cancer.

Early reports that breast cancer consistently enhanced whereas benign changes did not led some workers to suggest that MR imaging may be used to avoid a surgical biopsy (Kaiser and Zeitler, 1989). However, benign conditions such as fibroadenoma, sclerosing
adenosis, and fibrocystic changes do enhance and thereby reduce the specificity of contrast-enhanced MR imaging for the diagnosis of breast cancer. False positive contrast-enhancement (even when formal malignancy criteria of enhancement velocity are met) has recently been reported in normal healthy volunteers (aged 21 - 41 years) during all phases of the menstrual cycle, especially in weeks 1 and 4 (Kuhl et al, 1997).

False negative results of MR imaging present a serious dilemma because the patient may miss the chance for treatment of a curable lesion. These have been reported in studies that have had a higher threshold in defining a positive finding in an attempt to improve specificity. False negative cancers have mainly been invasive lobular cancers and DCIS (Gilles et al 1994a, 1995; Boetes et al, 1994, 1995; Orel et al 1994a, 1995; Bone et al 1996).

**MR imaging in cancer staging**

Several studies have shown an improved accuracy of MR imaging compared to mammography and ultrasonography for the measurement of the sizes of invasive tumours (Kerslake et al, 1995; Boetes et al 1995). Kerslake et al (1995) reported a lower correlation coefficient for invasive lobular carcinoma compared to invasive ductal cancers measurements. Boetes et al (1995) observed an extreme discrepancy in an invasive lobular cancer that measured 15cm on histological examination, but only 4cm of the tumour enhanced on MR imaging.

Harms et al (1993) correlated MR images of 30 patient with breast cancer with serially sectioned pathological specimens. MR imaging identified an additional eleven cancers that were mammographically occult. The lesions not seen at mammography ranged in diameter from 3mm to 12cm. Whitney et al (1993) reported that in 15 patients with 19 cancers seen on mammograms, 32 cancers were detected with MR imaging. In 10 patients multifocal cancers were detected at MR imaging, but in only four were they detected at mammography. In a series reported by Orel et al (1995), MR imaging depicted one or more cancers not visible at mammography in 22 (34%) of 64 patients studied. The improved sensitivity of MR imaging enabled a change in treatment in seven patients (11%). In a series of 61 mastectomy specimens analysed by Boetes et al (1995), 13 (20%) had multifocal invasive tumours, of which MR showed 100%, compared to mammography and ultrasound that showed 31% and 38% respectively.

Limited experience by some workers suggest that MR imaging may be of value in patients with metastatic axillary nodes but a normal clinical and mammographic examination. Historically, mastectomy has usually been the treatment of choice in this group of patients, despite the fact that in only two-thirds of these patients will a primary cancer be found at histopathological evaluation of the breast after mastectomy. (Baron et

**Ductal carcinoma in-situ (DCIS)**

The sensitivity of MR imaging for the detection of DCIS has varied widely in the literature. False negative cases of DCIS have tended to be slow enhancing lesions in studies using the rate of enhancement as the sole criterion for defining a positive finding (Gilles et al, 1994a, 1995a; Boetes et al, 1994, 1995; Stomper et al, 1995). In a series reported by Boetes et al, 7 of 8 DCIS lesions were correctly identified using the criterion of early enhancement defined as enhancement within 11.5 s of contrast-material injection. The false negative case of DCIS in the latter series showed delayed enhancement and was a 9cm tumour. Stomper et al (1995) using a section-selected gradient echo sequence, required a lesion to enhance 2 or more times than the unenhanced intensity to make a positive diagnosis. Using this criterion, the authors missed 2 cases of DCIS measuring 40mm and 60mm in diameter. Gilles et al (1995a), attempted to explain the mechanism for delayed enhancement in the two false negative cases of comedo type DCIS (8 mm and 20mm in size) on the basis of weak tumour angiogenesis. However, Hulka et al (1995) reported conflicting results of tumour angiogenesis in their two false negative cases of DCIS in their series using echoplanar imaging.

In contrast, studies using static contrast-enhanced techniques have report visualisation of all cases of DCIS (Harms et al, 1993; Heywang, 1994) using morphological criteria of focal or diffuse enhancement. In the series reported by Heywang (1994), using a 3D FLASH sequence, MR imaging identified all 15 cases of DCIS in a series of 150 cancers.

### 2.5.2 DIAGNOSIS OF LOCAL RECURRENCE WITHIN THE CONSERVED BREAST

The earliest series on the role of MR imaging in the diagnosis of local recurrence within the conserved breast was reported by Lewis-Jones et al (1991). In this series, the authors studied 45 patients but obtained histological confirmation in only 21 cases. MR imaging showed all 11 recurrent tumours giving a 100% sensitivity but 2 false positive studies resulted in a lower specificity of 94%. Recurrent tumour was best differentiated from scar tissue on T2W spin echo images where the tumour was of higher signal intensity in relation to area of fibrosis, although they appeared morphologically identical to each other. Intravenous gadolinium was used only in equivocal cases.

Further studies by Heywang et al (1990) showed that reliable distinction between scar and recurrent tumour was not possible in the first six months after surgery. In a further study
(Heywang et al, 1993), the same group reported that the breast treated with surgical excision and adjuvant radiation therapy exhibits rapid, intense signal enhancement in the first six months after therapy is completed, but with time both the rate and amplitude of contrast-enhancement diminishes such that no significant contrast-enhancement occurred in irradiated scar tissue beyond 18 months after radiation treatment. In this study only 17 of the 62 patients studied had histological confirmation for the presence or absence of local recurrence.

Other investigators using dynamic imaging techniques have used various criteria in diagnosing local recurrence. In a series reported by Gilles et al (1993), 14 patients with local recurrence were seen and all showed enhancement at 1 minute 34 s after injection of contrast agent. Dao et al (1993) defined a positive finding as lesions enhancing in the first 3 minutes after bolus administration of 0.2mmol/kg Gd-DTPA irrespective of its rate of enhancement. In this series, 26 patients were studies, of which 9 were confirmed to have local recurrence on MR imaging and surgical biopsy. In the remaining cases, with negative MR findings, no histological confirmation was obtained.

Dynamic imaging studies reported by other workers (Hickman et al, 1994; Kerslake et al, 1994; Murray et al, 1996) have all shown a sensitivity of 100% in diagnosing local recurrence using the criterion of early enhancement. However, these studies are based on few patients (4 - 5 patients) with histologically proven recurrences. Furthermore, histological confirmation of post-radiation changes in the patients that showed contrast-enhancement but below the selected cut-off points used to define early enhancement is not available in these studies.

As discussed earlier, dynamic contrast-enhanced studies have several limitations. To overcome the limitations associated with ROI analysis, Musarakis et al (1995) suggested multislice dynamic imaging with analysis of all components of time-intensity curves at several ROI. In this study, significant differences between benign and malignant lesions were found for the enhancement indices, maximum uptake, amplitude of uptake, wash-in rate, and wash-out rate of contrast agent. In this series, 57 patients were evaluated and recurrence was confirmed in eleven, of which all were diagnosed accurately using MR criteria. The authors suggest that synthetic (parametric) images can be produced based on the above enhancement parameters which will enable the original images to retain their spatial resolution while providing additional information about lesion permeability and vascularity, and helping to avoid the observer variability associated with ROI analysis.

Chemical-shift fat-suppressed images have not been proven to be of value in the diagnosis of local recurrence (Kerslake et al. 1994, Murray et al, 1996). However, in these studies, fat suppressed images were acquired approximately 10 minutes after contrast-medium injection, which probably contributed to the low specificity. Image subtraction
has been used by some workers, although its additional benefit over conventional post
contrast images has not conclusively been proven (Gilles et al, 1993; Murray et al, 1996)

2.5.3 ASSESSMENT OF RESPONSE TO NEOADJUVANT CHEMOTHERAPY

The value of MR imaging for the assessment of residual disease following neoadjuvant
chemotherapy was first reported by Gilles et al (1994b). Using similar dynamic imaging
protocol and interpretative criteria as in the diagnosis of primary breast cancer (Gilles et
al, 1994b), the authors were able to show residual disease on MR imaging in 17 of the 18
patients with one false negative study. The extent of contrast-enhancement correlated
with histological extent in 15 patients. Although, the authors suggest that subtraction
imaging facilitated visualisation of contrast-enhancement, respiratory and cardiac
movement diminished the quality of subtracted images in five patients. In three patients,
no lesion was seen on the T1W localiser images, and the section for dynamic imaging
was chosen according to the pre-treatment clinical drawing of tumour position. This
method further limits the accuracy of this study.

MR imaging with pharmacokinetic mapping of the changes in contrast-enhancement
following each cycle of chemotherapy has been investigated by Knopp et al (1994). This
showed that response to chemotherapy was associated with decrease in the rate of contrast
material uptake. However, no pathological correlation to the changes seen on MR were
undertaken in this study.

2.5.4 PROSTHESIS

Mammography has been used to evaluate breast implants and can show extracapsular
leakage of silicone adjacent to the implant (Destouet et al, 1992). Its limitations remain in
imaging leakage of small quantities, silicone remote from the implant, in the
differentiation of a small herniation through a weak area in the fibrous capsule in an intact
implant from extruded silicone due to rupture, and finally intracapsular ruptures.
Ultrasonography has similar limitations (Caskey et al, 1994)

MR imaging allows a more comprehensive evaluation of implants than that is possible
with ultrasound or mammography. It can accurately exclude the possibility of
intracapsular and extracapsular rupture, including in the area posterior to the implant
which is poorly shown by both mammography and ultrasound. In addition MR imaging
provides a more global view than ultrasound does, and free silicone can be detected in
areas remote from the implant (Weinreb and Newstead, 1995).
2.6 MR GUIDED BIOPSY

The finding on MR imaging of clinically and mammographically occult foci of enhancement have necessitated the development of MR biopsy systems. Most MR systems used for performing breast MR imaging are high field superconducting magnets. As such there is no access to the patient directly while the scan is being performed. This requires that the patient be removed from the magnet to gain access to any portion of the breast to perform needle biopsy.

Heywang et al (1994b) described the use of compression plates with series of holes and fiducial registration markings which are visible on the MR images. After the breast is imaged, the patient is removed from the bore of the magnet. The lesion is localised with the co-ordinates obtained from the MR images and, the biopsy needle is passed through the appropriate hole. The patient is then returned to the magnet to confirm needle position. A similar biopsy system with an additional external needle guide that can be positioned in three dimensions by means of positioning dials is described by Orel et al (1994b). The latter system allowed accurate MR guided needle biopsy of all clinically and mammographically occult foci (0.3 to 1.0cm in diameter).

The biopsy system described by Fischer et al (1995) uses an add-on device with surface coils. This system proved successful in performing an MR guided needle aspiration cytology in 82% of cases and positioning of non-magnetic hook wires for localisation biopsy in 92% of cases studied. Doler et al (1996) have described the only biopsy system in which the patient lies in a supine position. The surface coil used consists of two high semicircular hollow containers that are connected by a hinge. The coil design permits coverage of the whole breast. Each semicircular container has multiple puncture channels allowing the direction of the puncture needles to be adapted to the breast anatomy and location of the lesion. The size of the puncture channels also allows for core biopsy to be performed under MR guidance.

To overcome the problem of poor access and MR incompatibility of available biopsy devices and needles, Desouza et al (1996) have suggested using frameless stereotactic techniques in guiding biopsy of lesions seen on MR but without mammographic changes. In a small series of nine patients, needle placement within 2mm of the lesion was achieved at first pass in 89% of cases.

Although these reports may suggest that the procedure is fairly straight-forward, the localisation and biopsy techniques and devices will have to be refined and validated and users will have to be trained before they can achieve clinical application and accuracy comparable to that of stereotactic mammography needle biopsy. Non-ferromagnetic gauge needles for core biopsy are not commercially available, and the artefact associated
with 18-22 gauge needles makes it difficult to confirm the position of the needle tip within a small mass.

2.7 SUMMARY

Although the MR imaging techniques for breast evaluation continue to evolve, there appears to be consensus on some general requirements. Dedicated breast coils are necessary to achieve spatial resolution while maintaining high signal-to-noise levels. A contrast agent is essential for MR imaging to be sufficiently sensitive to breast cancer. Because the contrast agent currently available for clinical use do not remain confined to the intravascular space for very long, the benefits of increased specificity with their use are limited to the first few minutes after injection. This places temporal restrictions on imaging techniques in addition to the spatial resolution requirement for detecting small breast cancers.

With the use of contrast agent, gradient echo sequences have replaced spin echo sequences as the sequence of choice. Three dimensional volume imaging is preferred to two dimensional techniques and some form of T1-weighted sequence must be performed before and after injection of contrast agent. This review of the literature suggests that when low thresholds are used for the interpretation of MR images an excellent sensitivity (>95%), can be achieved for the detection of breast cancers but with a limited specificity.

A number of clinical situations have begun to emerge in which MR imaging of the breast may have a definitive role. At the time that the studies described in this thesis were initiated (June, 1994) most of the reports in the literature were based on heterogeneous group of patients including patients with breast cancer. These studies focused primarily on evaluating the sensitivity and specificity of MR imaging in the diagnosis of benign and malignant tumours but did not address specific problems or clinical situations where breast MR imaging should be used in additional to conventional triple assessment. The aims of our studies on breast MR imaging right at the start of this research project were to look at specific group of patients in whom MR imaging may provide clinically useful information compared with conventional triple assessment.
CHAPTER 3: BREAST CONSERVATION THERAPY

INTRODUCTION

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3.4 SUMMARY
INTRODUCTION

Several prospective randomised trials have compared mastectomy with breast-conserving surgery plus radiotherapy (Fisher et al, 1989; Sarrazin et al, 1989; Veronesi et al, 1990a; Jacobson et al, 1995). These trials, with follow up ranging from 6 to 13 years, have demonstrated no significant difference in overall survival and distant disease-free survival between the two treatment arms. The concept of breast-conservation is being taken a step further with the use of medical therapies (e.g. neoadjuvant chemotherapy, hormonal therapy, radiation therapy) as the primary and sole treatment for breast cancer. In addition, there is interest in the potential application of minimally invasive techniques for the localised ablation of primary breast cancer (Harries et al, 1994; Mumtaz et al, 1996).

This first section of this chapter reviews the principles and results of breast-conservation surgery, as these would need to be adhered to in the development of alternative treatments that are aimed at complete preservation of the breast without the need for surgery. In the second section of this chapter, medical therapies that have been used as the sole treatment of primary breast cancer and minimally invasive techniques that may have a role in the treatment of breast cancer are discussed.

3.1 BREAST-CONSERVING SURGERY

The aim of breast-conserving surgery is to achieve maximal cosmesis and minimal psychological morbidity, without compromising overall survival. Although the prospective randomised trials comparing mastectomy with conservative surgery plus radiotherapy have shown no significant differences in disease-free and overall survival, local recurrence is slightly more common after breast-conservation surgery (Fisher et al, 1989; Sarrazin et al, 1989; Veronesi et al, 1990a, Jacobson et al, 1995).

Local recurrence in the breast potentially undermines all the aims of breast-conserving surgery. Psychologically, a patient will lose confidence in the treatment, suffer the anxiety of cancer recurrence and may face the prospect of undergoing mastectomy or further aggressive surgery to achieve local control. Further surgery means that the cosmetic benefits of breast conservation are lost. In addition, when patients with local recurrence are analysed separately, association between such recurrence and shorter distant disease-free and overall survival have been reported (Fisher et al, 1991; Veronesi et al, 1995).

Local recurrence is thought to be due to residual multicentric disease left in the breast at the time for surgery for the primary tumour. The reported incidence of multicentric foci in breast cancer has varied from 18% when 1 - 2 random samples from each quadrant are examined (Spinelli et al, 1992) to 69% when 5mm sections of the whole breast were examined using Egan’s method (Egan, 1982). Holland et al (1985) evaluated the spatial
distribution of the additional tumour foci in relationship to the primary tumour in 282 patients treated by mastectomy. Residual invasive or in-situ disease was found in 59% of specimens at a distance of 1cm, in 42% at a distance of 2cm, in 17% at a distance of 3cm and in 10% at a distance of 4cm from the macroscopic edge of the tumour. These results have correlated closely with the incidence of local recurrence observed in clinical trials in which radiotherapy was not given. In the lumpectomy only arm of the NSABP-B06 trial, in which a 1cm clearance margin was taken around the tumour, the local recurrence rate was 53% at 10 years. (Fisher and Anderson, 1994). In the quadrantectomy arm of the Milan III trial, in which a 2 - 3cm clearance might be expected, the local recurrence rate was 8.8% at 3 years (Veronesi et al, 1993).

In a study reported by Vaidya et al (1996) also using the Egan’s method of whole organ analysis, the authors showed that multicentric foci were widely distributed in all four breast quadrants and that over 50% of these foci were present beyond 25% of the breast volume that contained the primary tumour (index quadrant). This finding suggested that multicentric foci may not contribute to early local recurrences as over 90% of the latter are known to occur in the quadrant that harboured the primary tumour. The authors suggest that recurrences in the index quadrant might arise from either the original primary tumour cells left behind rather than the multicentric foci or from circulating metastatic cancer cells lodging in the highly vascular bed of the excised tumour.

### 3.1.1 Factors predictive of local recurrence.

#### (a) Patient risk factor

Young patient age has consistently been observed to be associated with increased risk of local recurrence after breast-conserving surgery and radiotherapy (Boyages et al, 1990). However, his may be associated with the fact that in most studies, young patient age appears to correlate with adverse pathological features: grade 3 histology, absence of oestrogen receptors, and the presence of an extensive intraductal component (EIC). In a retrospective analysis from the M.D. Anderson Hospital, patients 35 years of age or younger did worse than older patients, but there was no difference in local recurrence, disease-free survival, or overall survival rates between young patients treated with lumpectomy and irradiation and young patients treated with mastectomy (Mathews et al, 1988). In a review of 1703 premenopausal patients with stage I to III breast cancer treated at Institut Curie between 1981 and 1985, young age (less than 34 years) was associated with poor outcome independent of type of local treatment (de la Rochefordiere et al, 1993). These data suggests that young patient is a prognostic factor, but does not seem helpful in selecting the best form of local treatment.
(b) Tumour risk factors

When comparing T1 (<2cm) and T2 (2-5cm) tumours, tumour size has little effect on the recurrence rate. In the two randomised trials with longest follow-up, patients with T1 and T2 tumours (Fisher et al, 1989) or with T1 tumours either less than or greater than 1cm (Veronesi et al, 1990a) had similar outcomes whether treated by conservation therapy or with mastectomy. Tumour location and axillary node involvement have also shown not to be predictive of local recurrence after conservation therapy (Boyages et al, 1990).

Studies have shown that local recurrence rates comparable with those of ductal carcinoma can be achieved with lobular carcinomas. Lobular carcinoma was not associated with an increase risk of local recurrence in the Milan or NSABP conservation trials. Some studies (du Toit et al, 1991) however, have reported increased incidence of local recurrence in patients with lobular carcinoma treated with conservation therapy. However, given the diffuse infiltration seen with invasive lobular carcinomas, a wide resection with clearly negative microscopic margins is generally advised. Experience with less common histological types such as colloid, medullary, and tubular, which are known to be more favourable with regards to survival suggest that the local recurrence is lower than that for invasive ductal carcinoma (Weiss et al, 1992). The presence of multiple macroscopic tumours is associated with higher local recurrence rate compared with a single macroscopic tumour (Kurtz et al, 1990). Multiple tumours are common in ElC-positive cancers and in the presence of lymphatic vascular invasion. Breast-conserving therapy is possible for patients with multiple tumours, only if these are in the same quadrant and negative margins of resection can be achieved.

The association between ElC-positive cancers and recurrence in the breast has been evaluated in a number of studies. In a retrospective analysis of 584 patients reported by the joint committee of radiation therapy, ElC-positive cancers constituted 28% of the invasive ductal carcinomas and were associated with 21% 5-year crude incidence of local recurrence. In the remaining EIC-negative cancers, the 5-year crude incidence of local recurrence was only 6% (p<0.0001). The corresponding 5-year crude incidence of distant or regional failure was 13% for EIC-positive cancers and 20% for EIC-negative cancers (Vicini et al, 1992). This data suggested that the higher rate of local recurrence in EIC-positive cancers is not because of a biologically aggressive form of breast cancer compared with EIC-negative cancers. Similar patterns of local failure were reported from Marseille Cancer Insitute who in addition observed that the association between EIC-positive tumours and local recurrence was seen only in premenopausal women (Jacquemier et al, 1990). In both studies patients were treated by limited excision of the primary tumour without attention to microscopic margins of resection.

Among patients treated in the Milan II trial with lumpectomy and radiation therapy, the 5-
year cumulative incidence rate of local recurrence was about 30% for patients with EIC-positive cancer and about 10% for EIC-negative cancer. In contrast patients treated by quadrantectomy and radiation therapy, the corresponding rates of local recurrence in EIC-positive and EIC-negative cancers were 10% and 5% respectively (Veronesi et al, 1994). In the series reported from Netherlands Cancer Institute (Borger et al, 1994), the overall 5-year actuarial local recurrence rate was 4%. Patients in this series underwent more extensive resection and received 75Gy radiotherapy which may account for the low rate of local recurrence. Young patient age, the presence of EIC, lymphatic vessel invasion, and involvement of microscopic margins of resection were all associated with local recurrence on univariate analysis. On multivariate analysis, the major risk factors were young patient age and the presence of vascular invasion. These results suggest that patients age and EIC are interrelated. Both factors are associated with local recurrence on a univariate analysis. Whether one factor or another or both persist on multivariate analysis may be related to the details of the extent of surgical resection, adjuvant radiotherapy and the role of margin assessment in patient selection for conservation therapy. The presence of EIC is not a risk factor for local recurrence after mastectomy (Rosen et al, 1986).

The higher incidence of local recurrence in EIC-positive cancers compared with EIC-negative cancers may be due to the high incidence of residual disease in the former group. In a study of mastectomy specimens by Holland et al (1990), the frequency of residual cancer in the breast after simulated gross excision was significantly greater for EIC-positive cancers than for EIC-negative cancers (74% versus 42%, P = 0.0001).

Lymphatic and vascular invasion are important pathological risk factors for local recurrence after conservation therapy. In the Milan overview of quadrantectomy, 6.5% of patients had lymphatic vascular invasion, and 24% of all recurrences occurred in this group. Locker et al (1989) found endolymphatic invasion in 24% of tumours, which strongly correlated with local recurrence, but this association was more pronounced in the first 2 years of follow up only. Both lymphatic and vascular invasion are known risk factors for local recurrence after mastectomy as well (Rosen et al, 1986). In addition they are also important prognostic factors with regards to survival in patients treated by conservation therapy or mastectomy. Thus lymphatic and vascular invasion are useful as prognostic indices rather than in selecting local treatment.

(c) Resection margins status

Various methods for assessing the completeness of excision have been suggested. The most widely used technique involves india ink staining of the specimen margins before cutting the specimen so that the margins can be clearly identified on microscopic examination. Other methods used in the assessment of completeness of excision include
multiple random biopsies from the cavity wall, a thin shaving from the entire cavity wall, cavity brushings and specimen scrape cytology. Umpleby et al (1988) demonstrated residual disease in 25% of patients using multiple tumour bed biopsies. Macmillan et al (1994) obtained a thin shaving from the cavity wall and demonstrated residual disease in 38% of patients. England et al (1994) compared specimen scrape cytology and tumour bed biopsies in assessing adequacy of wide local excision of breast cancer. Thirty nine (49%) of 80 cases were positive on specimen scrape cytology compared with 18 (23%) on tumour bed biopsies. Although these methods may increase the detection of incomplete excisions, they are all labour intensive and have a sampling error.

The definition of resection margin involvement has varied in the literature: positive margins indicating tumour transecting the inked margin and close margins defined as tumour found within 1, 2, or 5mm from inked surface. Gwin et al (1993) demonstrated residual disease in 65% of patients with a positive margin, in 23% of those with a close margin and in 45% where the margin status was unknown. Local recurrence rates at 5 years have been reported to be between 2 and 21% for patients with positive margins and 4 and 11% for those with close margins (Solin et al, 1991; Schmidt-Ullrich et al, 1989). Smitt et al (1995) showed that the attainment of negative surgical margins, initially or at the time of reexcision is the most significant predictor of local control after breast-conserving treatment with lumpectomy and radiation therapy.

(d) Treatment factors

The rate of local recurrence after conservation therapy potentially can be influenced by a number of treatment factors, including the extent of breast resection, the use of adjuvant radiotherapy, and systemic therapy.

The extent of breast resection required in breast conserving surgery is not universally agreed by surgeons. Beyond gross excision of the primary tumour, considerable controversy exists regarding the optimal extent of resection. In North America, a more limited resection is performed (lumpectomy), whereas in Europe a wider resection - wide local excision or quadrantectomy is performed. Increasing the volume of breast resection is associated with a decrease in the rate of local recurrence, but at the expense of an adverse effect on the cosmetic results (Veronesi et al, 1990b). As indicated above, a wider resection is advisable in patients with EIC-positive tumours, invasive lobular carcinoma and in younger patients.

Several randomised trials have compared breast-conserving surgery alone with breast-conserving surgery plus adjuvant radiotherapy. With follow-up ranging from 4 to 9 years, no significant difference in overall survival or distant disease-free survival between the two treatment arms has been observed (Veronesi et al, 1993, 1994; Whelan et al, 1994;
Liljegren et al, 1994). However, highly significant differences in the incidence of local recurrence were observed in all these trials. In addition, patients treated with inadequate doses of radiation therapy may be prone to local recurrence within the conserved breast (Osborne et al, 1984).

Evidence from the NSABP-B06 trial suggests that patients treated with conservation therapy who received adjuvant chemotherapy had a lower recurrence rate than those who did not (Fisher et al, 1989). In this trial, the effects of chemotherapy were assessed by indirect means because patients who received chemotherapy generally were node-positive, and patients who did not generally were node-negative. The NSABP-B13 trial, comparing outcome for node-negative patients who received chemotherapy with that of the no-treatment arm allowed a more meaningful assessment of the effect of chemotherapy on local recurrence. In this trial, 32% of the 579 patients were treated by conservation therapy. With a median follow up of 3 years, the rate of local recurrence in the breast was 7.4% in the no-treatment arm (conservative surgery plus radiotherapy only) compared with 1.7% in the patients who received adjuvant chemotherapy following breast conservation and radiotherapy (Margolese, 1992).

3.1.2 Cosmetic outcome after breast-conserving surgery

As mentioned earlier, a major goal of breast-conserving surgery is the preservation of a cosmetically acceptable breast. Although a variety of patient, tumour, and treatment factors have been reported to influence the cosmetic results, the amount of breast tissue resected seems to be the major factor. In the series reported by Veronesi et al (1990b), cosmetic results in patients treated by quadrantectomy were significantly inferior to those treated by lumpectomy. Matory et al (1990) observed that surgery was the main contributor to breast distortion in patients treated by breast conservation and adjuvant radiotherapy. In the latter series, the cosmetic outcome was graded by a general surgeon, radiation oncologist, and a plastic surgeon. The general surgeon and radiation oncologist rated 80% of the results as good or excellent, whereas the plastic surgeon considered only 50% to be good. However, the patients' assessment of cosmetic outcome correlated with those of the surgeon and radiation oncologist, suggesting that minor discrepancies in breast appearance are of limited significance.

3.1.3 Psychological outcome of breast-conserving surgery

A large number of studies have compared the psychological morbidity of mastectomy to that of breast-conserving surgery. These have shown either no significant differences (Fallowfield et al 1986), or in favour of mastectomy (Levy et al 1989) or in favour of breast-conservation (Lasry et al 1987). In the series reported by Fallowfield et al (1986), anxiety, depression or both were present in 38% of the women who had undergone breast
conservation compared with 33% of those who had a mastectomy. Fallowfield et al (1986) also noticed that 10% of patients treated with breast-conserving treatment developed obsessive checking of their breasts for recurrence. Levy et al (1989) prospectively evaluated 98 patients who chose their own form of local treatment. Seventy two percent of the patients chose breast-conserving surgery. At a 3 month follow-up visit, patients who chose breast-conserving surgery were found to be more distressed than patients who underwent mastectomy. In contrast Lasry et al (1987) reported significantly less depression in women treated with breast conserving therapy than in those treated by mastectomy as part of a randomised trial. These studies suggest that patients treated for breast cancer have psychological distress primarily related to the diagnosis and its implications, and that little is affected by choice of local treatment.

Although the operative procedure chosen does not seem to influence overall psychological outcome, most studies show an improvement in patients' body image and increased freedom of dress in patients undergoing breast-conserving treatment compared with mastectomy (Kiebert et al 1991).

3.1.4 Staging and treatment of the axilla

The evaluation and treatment of the axilla forms a vital part of breast-conservation surgery. The purpose of an accurate axillary evaluation is for staging breast cancer which provides a rational basis in guiding adjuvant therapy. Secondly, the histological status of axillary nodes in early breast cancer remains the single best marker of disease behaviour and ultimate outcome. Finally the treatment of the axilla is indicated to provide local control of the disease (Davidson, 1995).

The axilla can be evaluated surgically or by non-invasive imaging techniques. Currently available imaging techniques have limited sensitivity and specificity in showing axillary nodes involved with tumour including micrometastases and the number of positive nodes. The surgical evaluation of the axilla is undertaken either by axillary sampling or complete axillary clearance and proponents for each method exist (Greenall, 1995; Davidson, 1995). Sentinal node biopsy has been used to identify node-positive patients who may then benefit form complete axillary clearance for local control or quantification of number of involved nodes (Giuliano et al, 1994). It is beyond the scope of this thesis to discuss the merits and demerits of each method.

Some workers question the need at all for surgical evaluation of the axilla (Lin et al 1993). This is based on the fact that other factors (histological grade, DNA-ploidy, receptor status) may provide useful prognostic information and dictate the need for adjuvant therapy even in node-negative patients. Secondly, elderly patient receive adjuvant tamoxifen regardless of axillary status. Axillary dissection is not required in
patient with DCIS or DCIS with microinvasion.

The therapeutic role of axillary dissection is to maintain local control in the axilla. Complete axillary dissection provides excellent control for both clinically positive and negative axilla (Fisher et al, 1989). An alternate method of maintaining local control in the axilla is the use of axillary irradiation. Axillary recurrence rates of less than 3% or less have been reported in clinically node-negative patients undergoing breast-conservation surgery with adjuvant radiotherapy. The incidence of lymphoedema of the arm and breast after axillary radiation alone seems to be lower than after surgical dissection (Haffty et al, 1993). The axillary recurrence rate if the axilla is untreated is significantly higher, with up to 20% of patients requiring subsequent axillary dissection for disease progression. Although rare, axillary radiotherapy is associated with serious long-term complications that include brachial plexus neuropathy and radiation-induced sarcomas.

3.1.5 Patients suitable for breast conservation surgery

Patient selection for breast-conserving treatment involves an assessment of whether the primary tumour can be successfully removed with an acceptable cosmetic result, an estimate of the risk of local recurrence after breast-conserving treatment and mastectomy, and an evaluation of the patient’s desire and expectations. Evaluation of these factors requires a detailed medical history and physical examination, a detailed imaging evaluation to exclude the presence of other lesions and to help define the extent of the primary tumour, and careful pathologic evaluation of the resected specimen. The role of imaging techniques in the local staging of breast cancer and its value in treatment selection in patients with breast cancer is discussed in chapter 5.

It is important to appreciate that not all patients who are suitable for breast-conservation opt for this form of treatment (Kiebert et al, 1991) with some women, the percentage varying in different studies, preferring treatment by mastectomy. Patient preference alone, however does not explain the regional variation in the rates of breast conservation and surgeon bias is also an important factor (Osteen et al, 1992). Table 3.1 summarises the absolute and relative contraindications to breast-conserving treatment (Winchester and Cox, 1992).
Table 3.1: Indications and contraindications for selection of patients for breast conservation (adapted from Winchester and Cox, 1992)

<table>
<thead>
<tr>
<th>absolute contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>two or more gross tumours in separate quadrants of the breast</td>
</tr>
<tr>
<td>Diffuse indeterminate or malignant -appearing microcalcifications</td>
</tr>
<tr>
<td>History of therapeutic irradiation of the breast region</td>
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<tr>
<td>First or second trimester of pregnancy</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>relative contraindication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large tumour / breast ratio</td>
</tr>
<tr>
<td>Breast size sufficiently large to compromise adjuvant radiotherapy</td>
</tr>
<tr>
<td>Tumour location beneath the nipple</td>
</tr>
<tr>
<td>Collagen vascular disease</td>
</tr>
</tbody>
</table>

Patient suitable for breast-conserving treatment include those with a single clinical or mammographic lesion, measuring 4cm or less without signs of local advancement, extensive nodal involvement or metastases. There exist little debate over the absolute contraindication for breast-conserving treatment as detailed in Table 3.1. The suitability of large tumour for breast-conservation surgery is dependent upon the breast size and tumour location. In cases of tumour located beneath the nipple, although excision of the nipple-retroareolar area may be necessary, the patient is still left with a sensate breast and nipple reconstruction can be performed after completion of radiotherapy.

3.2 PRIMARY MEDICAL THERAPIES

3.2.1 Neoadjuvant chemotherapy

Preoperative chemotherapy or neoadjuvant chemotherapy has been used extensively for inoperable, locally advanced breast cancer to achieve tumour reduction and thus facilitate mastectomy or allow a breast preserving procedure to be undertaken. This is discussed in detail in chapter 7 of this thesis.

More recently, this strategy has also been studied in operable primary breast cancer, most commonly in patients with tumours 3cm or larger. Preliminary results from 2 randomised trials of preoperative chemotherapy have shown that local control was acceptable and survival longer in the neoadjuvant group (Mauriac et al, 1991; Fisher et al, 1994). In the
latter trial reported by NSABP, 1300 patients were randomised to neoadjuvant chemotherapy plus surgery versus surgery plus adjuvant chemotherapy. The response rate to preoperative chemotherapy was 80%, including 37% complete responses (CR). The CR rate was 50% for tumours less than 2cm or smaller and 18% for tumours larger than 4cm. More than 65% in the neoadjuvant group underwent breast-preserving treatment compared with 57% in the postoperative chemotherapy (Fisher et al, 1994).

3.2.2 Hormonal therapy

Concerns regarding the morbidity and mortality of conventional surgical therapy for breast cancer in the elderly patients with comorbid condition have resulted in a number of studies examining the efficacy of tamoxifen as a primary treatment.

Several prospective randomised trails have compared tamoxifen alone to some form of surgical therapy in elderly patients aged 70 years or older with operable cancer. Gazet et al (1994) randomly assigned 200 patients to undergo treatment with tamoxifen 10mg/day, or surgical resection without systemic therapy. At a median follow-up of 6 months, no difference in survival was observed between the two groups. However, local control was superior in the surgery arm: isolated progression of disease occurred in 56 of the patients in the tamoxifen arm compared with 36 of the patients in the surgery arm. In a larger study (381 patients) by Bates et al (1991), patients in the surgery arm also received adjuvant tamoxifen. At a median follow-up of 34 months there was an excess of local treatment failure in the tamoxifen group compared to the surgery plus tamoxifen arm (35% versus 13%). No differences were observed between treatment groups in the incidence of physical malaise, anxiety, social dysfunction, or depression. In a further follow-up at 42 months, Bates et al (1992) revealed a small but significant survival advantage for the surgery plus tamoxifen arm.

Although the operative procedures used in the trials do not represent the best available therapy, significant improvements in local control were seen in the patients treated with surgery in all studies. In addition, the use of primary tamoxifen treatment requires close follow-up for a number of years to monitor its response and local failures may require salvage surgery at a time when the patient may truly be unfit for surgery. Mastectomy is well tolerated in the elderly, and in one study the reported 30 day mortality rate was less than 2% (Morrow, 1994). In addition, no increase has been reported in the incidence of radiation side effects in elderly patients compared with younger patients treated with radiotherapy after tumour excision (Morrow, 1994). Tamoxifen as a primary treatment should only be reserved for the truly unfit elderly patient (Dixon, 1992).
3.2.3 External and interstitial radiotherapy (brachytherapy)

Radiotherapy for breast cancer began at nearly the same time as surgical treatment. Geoffrey Keynes in London was initially using radium needles to treat local relapse after mastectomy, and later extended their use to the treatment of operable breast cancer (Keynes, 1929). French radiotherapist Baclesse, at the Institute Curie, demonstrated that local control of relatively large tumours could be achieved using radiation dosages of 60 - 70 Gy given over up to 3 months (Baclesse, 1949).

Thomas et al (1988) reported 319 patients treated with radical radiotherapy alone (65Gy) who either had operable tumours but were unfit for anaesthesia or inoperable tumours due to local contraindication. In this series most patients had advanced tumours (less than 7 cm tumour in 21% of cases). The 5 and 10-year survival was 40% and 19%. The local and distant relapse-free rate was 56% and 33% at 5 years and 44% and 28% at 10 years respectively. Tumour size and histological grade were significant predictors of local response.

In the series reported by Gudea et al (1992), 164 cases of locally advanced breast carcinoma were treated with external beam irradiation (60 Co) of up to 45 - 50Gy supplemented with a boost, delivered either by interstitial 192 Iridium (30 - 40Gy) or by external irradiation with limited fields. The local failure rate was 31% (51 cases). The actuarial rate of survival with local tumour control was 53% at 5 years and 49% at 6.5 years, however distant metastases developed in 69 patients.

3.3 MINIMALLY INVASIVE TECHNIQUES

A number of minimally invasive techniques are currently being evaluated for the localised destruction of tumours within solid organs. These techniques can broadly be divided into two groups based on the primary mode by which they cause tissue necrosis.

3.3.1 Thermal treatments

(a) Radiofrequency interstitial thermal ablation

Radiofrequency interstitial thermal ablation is a technique in which heat is generated in the tissue around the needle or between the needles by molecular friction and ionic dissipation. The energy is delivered from radiofrequency-current generators via one or two electrode needles inserted percutaneously into the tumour. The temperature at the needle tip is maintained at 90°C for 120 s during a monopolar procedure, and for 20 minutes when using bipolar electrodes. The bipolar method achieves a volume of necrosis more than twice that of lesion made by simple unmodified monopolar needle. Eventual
drying of the tissue around the needle-tip causes a decrease in the current flow, and halting of thermal conduction (McGahan et al, 1990).

The technique has been applied clinically in the palliation of hepatocellular carcinoma and hepatic metastases of up to 3cm in diameter with promising results (Rossie et al, 1996). There is at present no report of its application in treating breast tumours. Percutaneous radiofrequency thermal ablation has the potential to be safe, cheap and effective alternative for the local in-situ ablation of solid tumours.

(b) High intensity focused ultrasound

This technique involves the use of ultrasonic energy generated by an external transducer which is brought to a sharp focus at a pre-determined depth within the body. The ultrasound waves are used at a frequency of 1 - 7.5 MHz and are capable of delivering greater than 100W/cm² of energy. This results in rapid tissue destruction in the focal zone within 1 second of exposure time. Focal coagulative necrosis is produced by thermal effects, although cavitation and tissue water boiling may occur (Hill and ter-Haar, 1995). Experimental studies in animal liver and tumour models have demonstrated that well-defined zones of coagulative necrosis can be reproducibly induced.

The technique offers the advantages of precise "trackless lesioning". Since the mechanism of tissue damage is primarily thermal in origin, the treatment can be monitored using temperature sensitive MR pulse sequences. Its disadvantage include the inability to potentially achieve complete tumour ablation, an observation reinforced by evidence both of in vitro cell survival and of tumour growth delay experiments. When attempts are made to ablate a block of tissue, by creating an array of adjacent elementary lesions, a phenomenon is observed of inhibition of formation of a lesion whose placing is too close to that of a neighbour (Hill and ter-Haar, 1995).

Clinical experience using this technique is currently very limited. A system for The MR guided focused US therapy has been investigated in gel phantoms and in vitro studies (Cline et al, 1995) and its potential role in the treatment of breast fibroadenomas is being evaluated by one group in Boston, North America (Pomeroy et al, 1995) although no detailed results have yet been published.

3.3.2 Non-thermal treatments

(a) Cryotherapy

This is an interstitial treatment and involves insertion of cryoprobes directly into the tumour. Tumour freezing is accomplished by circulating nitrogen at -196°C through the
inside of the probe (Bayjoo and Jacob, 1992). The response to treatment can be assessed by ultrasonography which shows the development of an enlarging echogenic "iceball" (Onik et al, 1986). Experimental studies in rabbit liver have shown that MR imaging may be useful in monitoring the response to cryotherapy (Matsumoto et al, 1992b).

Clinical experience of cryotherapy is mainly in the treatment of liver metastases (Bayjoo and Jacob, 1992). Its role in the primary treatment of breast cancers has not been evaluated as yet. The current bulky probe design (3-8mm in diameter) limits percutaneous insertion.

(b) Photodynamic therapy

Photodynamic therapy is a non-thermal technique for producing localised tissue necrosis with light-activated photosensitising compounds. Systemic administration of the photosensitiser results in its preferential accumulation in tumour tissue. This is followed by exposure to laser light at a wavelength matched to an absorption peak of the sensitiser, resulting in the generation of cytotoxic singlet oxygen resulting in cellular necrosis.

The application of photodynamic therapy in breast cancer has been limited to the treatment of chest wall recurrences following mastectomy (Lowdell et al, 1993) and experimental studies in breast cancer cell lines (Koechli et al, 1995). While these studies suggest the potential application of photodynamic therapy in the treatment of isolated chest wall recurrences, its role in the treatment of primary breast cancer has not yet been evaluated.

3.4 SUMMARY

Breast-conservation is a safe concept in the treatment of primary early stage breast cancer. The technique requires careful patient selection with the aim of minimising local recurrence and improved cosmetic outcomes. Careful patient selection is dependent upon imaging results including patients' preference for breast-conservation. Neoadjuvant chemotherapy is currently the most promising alternative treatment that may allow complete breast preservation in patients with complete pathological response.

A minimally invasive treatment that has been evaluated in some detail in the treatment of primary breast cancer is a technique known as interstitial laser photocoagulation (ILP). This is a percutaneous technique in which tumours are destroyed by direct heating using low power laser energy. ILP is discussed in greater detail in chapter 4 as it forms a part of the subject of this thesis.
CHAPTER 4: INTERSTITIAL LASER PHOTOCOAGULATION

INTRODUCTION

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4.9 SUMMARY
INTRODUCTION

Minimally invasive therapeutic procedures have been developed to reduce surgical trauma by exposing and isolating the smallest segment of the anatomy but still allowing access to the target volume with minimal injury. Such procedures necessitate shorter hospitalisation and offer potential cost savings. This concept combined with the known safety of breast-conservation has prompted research into the application of minimally invasive therapies to breast cancer.

Minimally invasive techniques that can effectively ablate a breast tumour including a margin of adjacent macroscopically normal tissue should theoretically result in similar local recurrence and survival rates as breast-conserving surgery. This approach would offer the advantages of preserving the size and shape of the breast, and reduce postoperative morbidity.

Interstitial laser photocoagulation (ILP) is a percutaneous technique of tumour destruction in which tumours are slowly heated to temperatures exceeding the threshold for protein denaturation, using low power laser energy delivered directly to the tumour via thin flexible optical fibres. ILP has undergone evaluation for over 10 years now. The clinical success of ILP is dependent critically on imaging modalities, since ILP is a percutaneous technique and the effects are therefore not directly visible. Improvements in lasers used for ILP have therefore been in parallel with technological advancements in radiological imaging techniques.

In this chapter, the principles of ILP and laser-tissue interaction will be discussed. A review is given of the relevant experimental and clinical data on ILP with emphasis on the advancement in imaging modalities used in guiding ILP.

4.1 PRINCIPLES OF ILP

The concept of interstitial laser therapy was first described by S.G Bown (Bown, 1983). The idea is very simple. Instead of delivering light from a non-contact fibre or by a fibre tip in contact with the tissue surface, the fibre is inserted directly into the target organ. The potential advantages of such an approach over external therapy included: direct thermal contact with a much larger volume of tissue, all energy transmitted down the fibre is absorbed in the tissue (apart from the very small amount reflected back up the fibre) in contrast with external therapy where the precise amount of energy absorbed depend on the surface under the beam, minimal surface effect apart from the tiny hole requires for fibre insertion, and protection of the fibre tip as larger quantity of energy are required to heat the tip sufficiently to damage it. Within the tissue, the fibre tip acts as a point source of energy, and the distribution of effects around it are roughly spherical. In his landmark
paper, Bown (1983) described interstitial laser therapy of two metastatic cutaneous deposits using a power of 5 - 20W for a duration of 10 s to 15 s.

When the optical fibre-tip is buried in tissue, the response occurs in a very confined space. If the energy delivered is too fast, the result can be a mini-explosion. An excessive amount of tissue water may be vaporised, and since there is nowhere for this to escape, local pressure disruption of tissues may occur; also, the fibre-tip can be damaged if it gets too hot while in contact with biological material. Thus, interstitial therapy is best carried out at very low laser powers (less than 5W) for a prolonged period of time (typically 8 - 10 minutes).

4.2 LASER-TISSUE INTERACTION

The word “laser” is an acronym that stands for light amplification by stimulated emission of radiation. Laser light has three unique qualities: it is monochromatic (all waves are in the same wavelength), coherent (the waves are in phase with each other) and collimated (the waves are exactly parallel to each other). These properties allow laser light of appropriate wavelength to be delivered in a precise, controlled and predictable manner to a very small area.

4.2.1 Mechanism of action of ILP

In the developing phase of ILP, it was assumed that the deeper the penetration of laser light into tissue, the greater is the amount of absorbed laser energy and hence the extent of thermal damage. Based on this theoretical assumption which had not been tested experimentally, the excellent tissue penetrating properties of the 1064nm wavelength neodymium yttrium aluminium garnet (Nd:YAG) laser light combined with the fact that Nd:YAG laser light can easily transmitted down thin flexible fibres made it a popular choice for use in ILP (Bown, 1983; Svaasand et al, 1985; Mathewson et al, 1987).

An alternative mechanism of action of ILP was first proposed by Steger et al (1991). The authors suggested that charring seen at the fibre tip during ILP focuses the laser energy at the fibre tip, which then acts as point heat source, and subsequent necrosis occurring by thermal conduction into tissues. This proposed mechanism of action was subsequently evaluated in detail by Amin et al (1993a). Experimental studies undertaken in rat liver showed that less penetrating wavelengths (1320nm, 805nm, 484/514nm) can cause greater thermal damage during ILP than 1064nm. Secondly, the extent of thermal necrosis could be increased with 1064nm wavelength only by precharring the fibre tip.

During ILP with the 1320nm and 805nm wavelengths, charring in liver tissue occurs relatively quickly and at low powers, compared with the 1064nm wavelength. This is
likely to be due to the energy being deposited in a much smaller tissue volume around the fibre tip, resulting in higher temperatures (Svaasand et al, 1990). Once charring has occurred, a positive feedback begins, with even less light penetration, higher local temperatures and more charring. Pre-charring the fibre tip allows this cycle to be initiated with the 1064nm wavelength, with a subsequent dramatic increase in the size of necrosis. The size of necrosis in the presence of charring may be independent of laser wavelength (Amin et al, 1993a). With the onset of charring, the laser is essentially acting as a point heat source rather than a distributed heat source (point optical source) in the absence of charring. Tissue heating and consequent necrosis then occurs as a result of thermal conduction rather than light penetration and the extent of thermal damage depends on the temperature gradient achieved as well as the length of time the tissue is exposed to the elevated temperatures (Thomsen, 1991).

4.2.2 Effects of heat on tissues

The extent of thermal necrosis occurring in tissues is dependant on the thermal and optical properties of the target tissue (Svaasand et al, 1985) and the wavelength of laser light which determines the volume in which the energy is absorbed. (Blanc and Colles, 1990). It is the absorbed energy which produces biological effect, but reflection, transmission and scattering determine where the light goes, and consequently the volume of tissue in which it is absorbed. The tissue changes which take place are related to the temperatures reached and the time for which the tissue remains at these temperatures. These factors have been called the “thermal history” of the tissue (Thomsen, 1991).

At energy density less than 4J/cm² (below the thermal threshold), the effect of laser light are biostimulatory; stimulation of wound healing by increasing collagen synthesis and capillary regrowth (Mester et al, 1981). Laser light at low or very low intensity would therefore be counter-productive in tumour therapy. If a large tumour mass is being treated, the laser light intensity may drop to give absorbed energies of this level (< 4J/cm²) at some distance from the main beam which could stimulate rather than repress tumour growth. There is some evidence that this might happen in practice. Gradner et al (1982) showed that solid mouse tumours, treated with sublethal dose of light from a Nd:YAG laser, regrew from the edges at a slightly faster rate than controls. At energy densities greater than 4J/cm², the effect of laser light are biosuppression and range from nonthermal cytotoxic phototherapy, photocoagulation and vaporisation with increasing levels of energy and power density.

During ILP, a temperature gradient exists from the fibre tip towards the tissue periphery (100 - 200 °C at the fibre tip to 50 - 60°C about 7mm from the fibre tip) giving rise to well defined zones of tissue effects. However, it must be emphasised that the three-dimensional temperature distribution in tissues during ILP is not uniform, particularly in
proximity to large blood vessels (Matthewson et al, 1987). At temperatures below 45°C typically seen during hyperthermia, tissue effects are only produced over a long time (30 minutes to several hours) and are often reversible. They include mitotic arrest, decreased cell metabolism, fall in cellular oxygen and pH, and changes in local blood flow (Sisken et al, 1965). Immediately after treatment, low temperature cell and tissue thermal injury cannot be seen on macroscopic and conventional light microscopic examination and require the use of special histological techniques such as enzyme histochemistry and transmission electron microscopy for accurate mapping of tissue necrosis. In most cases, the full extent of tissue necrosis cannot be mapped on conventional light microscopy until 48 - 72 h after treatment (Thomsen, 1991).

At 45-99°C there is irreversible denaturation of tissue proteins and coagulation occurs. In this temperature range an inter-relationship exists between the tissue effects and the duration of exposure at that temperature. Temperature need only exceed 47°C for cellular necrosis to occur when treatment times are approximately 10 minutes (Thomsen, 1991). At temperatures greater than 100°C tissue water boils; the conversion of water to steam results in a thousand-fold expansion and the cell walls rupture, allowing steam to escape. During ILP, with the heating occurring in a closed space, the steam escapes along tissue planes and into any adjacent blood vessels. Once the water around the fibre-tip has dried, the temperature will rapidly rise to 300-400°C, with subsequent tissue blackening, carbonisation, tissue loss and smoke production (Pearce, 1990).

4.3 LASERS FOR ILP

There are several types of laser, each producing light of a specific wavelength in the electromagnetic spectrum; 10600nm carbon dioxide laser, 1064nm and 1320nm Nd:YAG laser, 805nm diode laser, and 488nm and 514nm Argon ion laser. All except the carbon dioxide laser have been evaluated for ILP. The carbon dioxide laser has poor tissue penetration (0.1mm in soft tissue) and heats a very small volume of tissue. The highly localised effect makes it suitable as a surgical knife. It cannot be safely transmitted down flexible fibres; currently available fibres are toxic, expensive and relatively inefficient which makes its application for ILP useless.

The 1064nm Nd:YAG laser was the most widely used for ILP until 1993. This was based on its excellent tissue penetrating properties, transmission down flexible fibreoptics, and wide availability due to its role in external non-contact mode treatments. Subsequent work by Wyman et al (1992) and Amin et al (1993a) showed that ILP might be equally well or better performed at wavelengths that are absorbed more effectively than near infrared.

Amin (1993) compared 1320nm Nd:YAG, 805nm diode, 488/514nm Argon lasers with
1064nm Nd:YAG laser. The author observed that using similar fibre tips, the 1064nm wavelength produced less necrosis than all other laser wavelengths. The 488/514nm Argon laser was associated with mini-explosions and significant surface effects due to unpredictable forward channelling of the light beam. There was little difference between the 1320nm and 805nm wavelengths with respect to the final size of necrosis.

Currently the most common lasers used for ILP are the 805nm semiconductor diode lasers (Amin, 1995; Ripley, 1996). These devices have a high electrical - to - optical efficiency which has allowed them to be made light weight, compact and to operate from a standard alternating current electrical outlet with a relatively high power output. These features have made them more attractive to clinicians and very suitable for use in different imaging suites compared to Nd:YAG laser which are bulky and require water cooling. The disadvantage of diode lasers has been the their power output a maximum of 25W, however this has recently been improved to 60W (Amin, 1995) which may also allow their use in other non-contact mode medical applications.

4.4 LIGHT DELIVERY SYSTEM

Laser light is delivered to tissues via thin optical fibres. The laser light is transmitted down the fibre by total internal reflection with minimal power loss and fibres can be made as long as required. A typical optical fibre consists of a central core which is covered by a layer called the cladding. For fibre operation it is necessary that the refractive index of the fibre core is greater than the outer cladding. A fibre consisting just of a core and cladding is very fragile and needs to be surrounded by a buffer coating or jacket to improve its mechanical strength and to reduce the permitted bending radius (Verdaasdonk and Borst, 1995). There are three types of optical fibres for medical use and their main difference is in the type of cladding around the core. The core of all three types of fibres is made of fused silica, and it is the diameter of the core which is normally quoted. The buffer coat is usually made of nylon or acrylate. It is the cladding material that distinguishes the fibre types; plastic, hard polymer, or silica.

The tip of the laser fibre is the plane cut glass end of the fibre revealed by paring back the cladding (Amin, 1993). The bare fibre tip acts a point source of heat during ILP. The fibres are inserted into tissues through hollow metal needles passed percutaneously. Various modifications to the bare fibre tip have been described with the aim of increasing the surface area from which the light is emitted. These modified fibre tips provide a distributed heat source and can withstand relatively higher power before charring is initiated at the fibre tip. The experimental and clinical evaluation of the two fibre tip types is discussed in the section below.
4.5 EXPERIMENTAL STUDIES

Experimental studies in liver tissue have provided the main data on the optimal laser and optical fibre parameters required for ILP. The following section reviews the experimental studies of ILP performed in normal liver.

4.5.1 Bare fibre-tip work

ILP has been performed in *in vivo* normal rat, rabbit and pig liver (Matthewson et al 1987, Dachman et al 1991, Matsumato et al 1992). The earliest and most comprehensive work was performed by Matthewson et al (1987) in rat liver, using a 0.4mm optical fibre. Well-defined, symmetrical and reproducible necrotic lesions up to 16mm in diameter were found, which increased in size with increasing power and energy, although there was a plateau effect above a power of 1W and energy of 600J. Above 0.75W charring around the fibre-tip was almost universal even for exposures as short as 200 s, but was reported as being disadvantageous. Temperatures of up to 100°C were recorded at the fibre-tip, dropping to 52°C 8mm away, using a power of 2W. The relative light intensity 4mm away from the fibre-tip fell to 27% of its initial value after a 200 s exposure at 2W, which was thought to indicate the changing optical properties of liver during ILP, but may in fact also be due to fibre tip charring. Arteriography demonstrated loss of all small and some large (up to 1.5mm diameter) vessels in the treated area. The diameter of the necrotic zone was maximal about the seventh day, after which progressive resolution occurred with the formation of a small fibrotic lesion at 60 days.

Similar extent of necrosis was shown in rabbit liver by Matsumoto et al (1992a), who also showed that the longitudinal (along the fibre-track) diameter measured greater than the transverse (perpendicular to the fibre-track) diameters of necrosis (17mm and 13mm, respectively) producing an ellipsoid lesion. Increasing the power resulted mainly an increase in the longitudinal diameter with minimal effect on the transverse diameter. The transverse diameter of the laser induced lesion could be increased by advancing the fibre tip rather than keeping it in a fixed position as this allows the tip to be in contact with histologically unaltered tissue. Higuchi et al (1992) used slightly higher powers up to 9W for ILP to rat liver and observed similar changes in the respective diameters of the necrotic lesion: the transverse diameter plateauing at 2W, and the longitudinal diameter at 9W respectively.

Further experimental studies by Amin et al (1993a) evaluated in detail the laser and optical fibre parameters used in ILP and highlighted the significance of charring which in earlier experiments was thought to be disadvantageous. The laser wavelength and the significance of charring is discussed in the section on mechanism of ILP. Evaluation of the optical fibre parameters showed that plastic clad and precharred fibre tips were
significantly associated with greater diameter of necrosis, although the data did not conclusively show this to be independent of laser wavelength and power. The use of metal needle tips connected to the standard optical fibre showed significantly greater necrosis and charring compared to bare fibre tip. The disadvantage of metal needle tips is the risk of them sticking firmly to charred tissue. In addition this fibre tip modification resulted in unpredictable proximal propagation of necrosis and damage to fibre jacket and cladding.

4.5.2 Multiple fibre-tip work

In order to safely increase the volume of tissue necrosis, and still use one laser as the energy source, beam splitters or fibre-optic coupling systems have been used (Steger and Bown, 1989). These allow simultaneous activation of several optical fibres. The system initially tested (1x4 Star coupler - Canstar, Canada) allowed equal splitting ratios from a single input optical fibre to 4 output fibres, and although the power outputs remained stable there was loss of up to 40% of the input power at the fibre junctions particularly at powers greater than 10W (Steger et al, 1991). The 1x2x4 optical splitter designed by Diomed (Diomed, Cambridge, U.K) appears to be more reliable (Amin et al, 1993b).

Experimental studies in normal canine liver using four fibres by Steger et al (1992a) showed that the optimal parameters for producing uniform overlapping necrosis were a power output of 1.5W per fibre, an exposure time of 670 s, and fibre-tip spacing of 1.5cm positioned approximately at the 4 corners of an arbitrary square. This set-up gave well-defined, spherical necrotic lesions of up to 4cm in diameter. Tissue charring was consistently seen at the sites of the fibre-tips, and the recorded temperature in the centre of the necrotic lesion (10mm from the fibre-tips) was 60°C after 500 s of ILP. There was one complication of an hepatic abscess one month after ILP. Liver angiography showed a clear zone of devascularisation in the treated area with no arterial supply to the laser-induced thermal necrosis. Healing occurred safely and by 1 year, only 4 small chars remained in normal liver.

4.5.3 Modified fibre-tip work

Various diffuser fibre-tips have been used in an attempt to increase the surface area from which tissue heating occurs and provide a distributed heat source without charring. Proponents of a distributed heat source (van Hillegersberg et al, 1995) claim that although at the same (lower) power output a point heat source may produce a larger lesion (with charring), the former can heat a larger area from the fibre tip due to a less steep temperature gradient. Nolsoe et al (1992) designed a diffuser fibre tip by grinding the distal 2-3mm of the quartz core of a bare optical fibre, to give a cone shaped frosted tip. Using higher levels of energy delivery (4W, 600 - 2400 s) Nolsoe et al (1992) in *ex vivo*
porcine livers produced significantly greater diameter of necrosis (23.5 - 44mm) compared to bare fibre tip (15mm). At higher energy delivery, charring and cavitation occurred but zone of coagulation continued to increase as the energy increased.

However, experimental studies reported by Malone et al (1992) comparing plane-cut bare fibre-tips, and specially designed cylindrical diffusing fibre-tips and spherical diffusing fibre-tips showed that the bare fibre-tips produced much more effective necrosis than the diffusing tips, the latter being unable to withstand powers of 3-6W. van Hillegersberg et al (1994) described a specially designed cylindrical diffuser tip with a scattering coating. The maximal lesion size at 2W, energy 2400 J was only 11mm which is comparable to previous studies using combined ablation and coagulation (accompanied by charring). The maximal width of laser necrosis was directly related to the laser energy applied with charring occurring at higher power.

In summary, most of these studies have shown that most modified fibre-tips are no better than bare tips for ILP except the report from Nolsoe et al (1992).

4.6 HISTOLOGICAL FEATURES OF ILP

The histological features of ILP immediately after treatment in normal liver, brain and tumour models are broadly reported as a central zone of cavitation and charring at the fibre tip, beyond which is a zone of coagulative necrosis. (Matthewson et al, 1987; Matsumoto et al, 1992a; Tracz et al 1992). Matthewson et al (1987) described the latter zone as a region of degeneration which progressed to frank necrosis at 24 h with an inflammatory response at its margin. By 4-7 days, granulation tissue is apparent in the periphery of the lesion, with infiltration of neutrophils, giant cells and macrophages, and some tissue regeneration (Matthewson et al, 1987; Bosman et al, 1991; Tracz et al 1992). This is replaced by a small fibrous nodule with some residual central carbonisation at 3 - 8 weeks after treatment (Matthewson et al, 1987).

In ILP of normal rat liver, Amin (1993) observed that within the zone of coagulative necrosis was a zone of fairly well preserved hepatocytes with intact nuclear and cytoplasmic membranes defined as the zone "in-situ" fixation. The only abnormality seen in these cells on Haematoxylin and Eosin (H&E) staining was mild cytoplasmic pallor and fine vacuolation. Beyond this zone until its junction with normal liver, the cells showed features of necrosis that were evident on H&E staining. Diaphorase staining was of value in evaluating the extent of necrosis in lesions immediately after treatment as these showed a charred cavity with little morphological changes in its periphery on H&E staining. The boundaries of the ILP induced lesion were similarly defined on H&E staining and diaphorase staining 24 h or more after ILP.
4.7 IMAGING OF ILP

For ILP to be safe, it is essential to be able to predict the nature, extent and healing of the tissue damage that given laser parameters will produce since it is impossible to assess the results of ILP by any immediate visual effects or predict the extent of tissue necrosis based on laser parameters. The latter may in part be related to biological variability (Cheong et al, 1990), fibre-tip deterioration during ILP, and changing optical and thermal properties of the tissue during ILP (Svaasand et al, 1985). However, more important, is the detection of residual tumour after ILP which will reflect the true success rate of interstitial treatment. Thus real-time monitoring of thermal effects during ILP and accurate assessment of the full extent of necrosis and residual tumour after ILP are very important for its success.

Thermocouples give only single point temperature measurements rather than a three dimensional map of the evolving thermal lesion, and are of relatively little value clinically because they are invasive and may absorb light and contribute to tissue heating (Philipp et al, 1993); in addition, intra-tumoral temperatures have a non-uniform distribution during heat treatment (Fessenden et al, 1984). Imaging provides a non-invasive way of monitoring the tissue changes during and after ILP. Experimental and clinical studies have evaluated ultrasound (US), computed tomography (CT), and magnetic resonance (MR) imaging of ILP.

4.7.1 ULTRASOUND (US)

4.7.1.1 Experimental studies

All experimental studies investigating ultrasound monitoring of ILP initially reported good imaging-histopathological correlation (Dachman et al 1990; Bosman et al 1991; Malone et al 1992; Steger et al 1992b) and were reported in dog or pig normal livers. There appears to be a general agreement in the ultrasonographic changes seen during ILP. This includes the appearance of areas of increased echogenicity at the fibre tip with irregular, spherical or star shaped margins. The first appearance of the echogenic zone has varied from 30 s (Steger et al, 1992b) to 120 s (Bosman et al, 1991) from the start of laser activation. The size of the developing echogenic zone reaches a plateau by 300 - 400 s into treatment. Also seen during therapy are irregular echogenic streaks radiating away from echogenic zone and trails of microbubbles seen "washing" away in nearby vessels (Amin, 1993). The irregular shaped expanding echogenic zone seen around the fibre-tip may be due to tissue water boiling and microbubble formation (Thomsen, 1991). Similar changes in ultrasonographic appearance were observed with multiple fibre therapy (Steger et al, 1992b). An echogenic star was seen at each fibre tip , the gap between these zones reduced to 3mm by 200 - 400 s into treatment and thereafter merged into a single
echogenic zone. Ultrasound images taken immediately after ILP tended to overestimate the size of necrosis, but later images (2 h after ILP) better approximated the true extent of necrosis with a tendency to slightly underestimate the actual size (Malone et al, 1992).

During healing, the echogenic lesion decreases in size over several weeks and also develops a more echogenic rim due to inflammatory repair and fibrosis (Dachman et al, 1990; Bosman et al, 1991). Good correlation of the size of the echogenic lesion on ultrasound with pathological size has been reported, at the end of ILP and at various times after ILP (Bosman et al, 1991; Steger et al, 1992b) although no statistical correlation have been shown.

4.7.1.2 Clinical studies

Amin et al (1993b) observed similar ultrasonographic changes during ILP of hepatic tumours as reported by Steger et al (1992b) in normal liver animal studies. However, in contrast to the findings in animal studies (20 s delay), there was a delay of 100 s before any ultrasonographic changes were seen during ILP of hepatic tumours in patients. In addition, the echogenic zone seen during and after treatment was not accurate in predicting the extent of tumour necrosis and residual tumour. Real time ultrasonography appeared reliable in predicting the extent of necrosis in small hepatic tumours (< 3 cm) but was grossly inaccurate in monitoring ILP of larger tumours. In addition, ultrasound was found to be of limited value at follow-up as there were no distinctive features differentiating necrotic from viable tumour tissue. This similarity between treated and untreated tumour made subsequent targeting of residual tumour difficult and was the main reason for not achieving complete tumour ablation despite several treatments performed under US guidance (Amin et al, 1993b).

In the series reported by Harries (1994), US was used in real time to monitor ILP in 43 patients with breast cancer. Although US allowed correct needle placement and measurement of tumour size before treatment, it was unable to accurately show tumour margins in five patients. The ILP changes seen during real time ultrasonography were similar to those reported by Steger et al (1992b) in the ILP of normal canine liver. The author also observed a poor correlation between the maximum size of the echogenic zone during real time imaging and the histological extent of necrosis (r=0.3). In this series, changes seen on follow-up ultrasound in the interval prior to surgical treatment of the breast cancer were not fully evaluated.

In summary, ultrasound is limited by the fact that it is essentially imaging microbubbles, and is unlikely to depict thermal damage if temperatures are not high enough to cause microbubbles but are still adequate for cell death. Furthermore, the field of view may become distorted with echogenic streaks. Immediate post ILP images are unable to
differentiate areas of tissue necrosis from residual viable tumour making subsequent treatments difficult. Ultrasound is also operator dependent, and the varying level of correlation shown in the above studies may in part be a reflection of operator's experience. In addition, the plane of ultrasonographic imaging and the plane of histological measurements are difficult if not impossible to match for accurate correlation. Ultrasound is useful in tumour localisation, although this may also prove difficult occasionally.

4.7.2 COMPUTED TOMOGRAPHY (CT)

4.7.2.1 Experimental studies

Amin (1993) correlated the tissue density changes on CT with the extent of necrosis seen on histological examination following ILP in *ex vivo* normal rat liver. The authors observed that size of necrosis measured on CT at 24 hours and 2 weeks after ILP correlated closely within 1-2mm with the actual zone of necrosis measured pathologically (histological measurement was performed in the plane and line of the marker placed on the rat liver). The technique of CT imaging appeared to be critical in accurately showing the area of necrosis. Dynamic CT (performed after a rapid intravenous bolus of iodinated contrast medium with scanning started 50 - 60 s after the start of contrast bolus) provided significantly greater liver-to-lesion contrast compared to delayed CT (performed 2 - 3 hours after contrast-material injection).

4.7.2.2 Clinical studies

In the clinical studies reported by Amin et al (1993b), the optimal time to obtain a post ILP CT was observed to be 24 h after treatment. Immediate post-treatment dynamic CT in two patients showed a vague low density zone within the treatment site which partially enhanced, however dynamic CT scans taken at 24 h or 72 h after ILP showed treatment effects as well defined new areas of non-enhancement. This non-enhancing zone was clearly differentiated from normally enhancing adjacent liver parenchyma and partially enhancing residual tumour. The interpretation of the non-enhancing zone as indicative of tissue necrosis is based on the finding in experimental studies as described earlier. In addition core biopsies from the non-enhancing and partially enhancing zones confirmed the presence of necrotic tissue and residual tumour, although it appears that these biopsies were performed with US guidance, which as earlier indicated may be unreliable.

Harries (1994) evaluated ILP in six patients with breast cancer using CT. In two patients, ILP was imaged by real-time CT during which an iodinated contrast agent was given 2 minutes after laser activation, followed by a 2-3 minutes delay to allow the contrast to circulate and then scanning undertaken of the treatment, being completed at the same time...
as the laser treatment. In one patient, although some changes were observed on real-time images, these were difficult to see on CT. In the second patient no changes were seen at all. In fact the laser fibre had passed through the tumour into the pectoralis muscle which was also not visualised on CT. In addition, there was also considerable artefact at the needle tip which made assessment difficult of changes seen on real-time CT. In four patients, dynamic contrast-enhanced CT obtained 24 h following ILP showed laser-induced necrosis as an area of reduced enhancement. This correlated with histological necrosis within 4mm in all patients. The study did not however evaluate the CT features of residual viable tumour or accurately correlate the changes seen on CT with histology.

In summary, dynamic CT as described by Amin (1993) can accurately show the laser treatment effects, allowing the technique to be considered as the "gold standard" in evaluating ILP lesions particularly in lesions that are not amenable to detailed histological evaluation.

4.7.3 MAGNETIC RESONANCE (MR) IMAGING

MR imaging is a three dimensional multiplanar technique that provides information from beneath the surface of the treated volume, is noninvasive and non-ionising. The optical fibre and light are not affected by the magnetic field used for MR imaging, nor does the optical fibre disturb the MR signal. MR imaging can reveal laser-issue interactions because laser irradiation changes not only the thermal motions of hydrogen atoms within the tissue but also the distribution and mobility of water and lipids. The MR signal depends on the structure and dynamics of water-macromolecular interactions (Bottomley et al, 1984). Laser energy causes macromolecules to denature, this changes both the number of water molecules in the bound and unbound states and the amount of time spent by water in each state. Changes in mobility of water results in changed relaxation rate.

The strong temperature dependence of MR relaxation has been studied in quantitative investigations (Barroilhet and Moran, 1975; Parker et al, 1983). At the field strengths used in these studies, the principal effect of temperature increase was an increase spin-lattice relaxation time T1. At temperatures greater than 40 °C, however an irreversible decrease in T1 has been reported (Lewa and Majewska, 1980). This can be attributed to alteration of macromolecule-water interaction which occurs before the obvious denaturation of proteins at 60°C.

4.7.3.1 Experimental studies: Dynamic imaging

The earliest work on MR imaging of laser-tissue interaction by Jolesz et al (1988) illustrated the concept of reversible and irreversible changes of MR signal intensity during and immediately after ILP. The experiments performed in egg white, minced
rabbit brain, *in vitro* rabbit head, and *ex vivo* mouse tumour showed an expanding zone of complete signal loss at the fibreoptic tip and decreased signal intensity around it on T1-weighted (T1W), T2-weighted (T2W), and proton density spin-echo sequences. Images taken after the irradiation demonstrated that the observed halo of decreased signal intensity around the residual structural lesion was reversible. The zone of irreversible signal loss was interpreted as being due to tissue water loss and altered tissue water mobility, while the surrounding reversible signal loss indicative of the effect of rise in temperature. Further observations in these experiments showed that at low energy (315 J), both T1 and T2-weighted signal intensity changes showed a hysteresis of the signal intensity versus temperature curve. At higher energy (1610 J), the change in T1 was irreversible. These results suggested that MR imaging has limitations as a tissue thermometer but the reversible changes in signal intensity may be useful for planning laser treatment, since the spatial distribution of reversible thermal effects may correlate with that of irreversible changes in the tissue.

Similar observations on signal intensity changes, including reversible signal loss during ILP of normal tissues have also been noted by others in *in vitro* and *in vivo* animal studies, using T1-weighted standard spin-echo (Higuchi et al, 1992), fast spin-echo (Matsumoto et al, 1992, 1994), gradient-echo (Marchesini et al, 1992) and T2-weighted proton spin echo sequences (Tracz et al 1992, 1993). The maximum size of signal loss on T1W images was found to roughly correspond to the extent of necrosis induced by ILP (Marchesini et al, 1992; Matsumoto et al, 1992), although its boundaries were not clearly demarcated because of the gradual rather than abrupt decline in temperature at the transition between necrotic and normal tissue. Tracz et al (1992, 1993) monitored ILP in normal cat brain using a T2W spin echo sequence which showed a region of complete or near complete signal loss that underestimated the actual lesion at 48 h.

Muller et al (1992) proposed using sequence parameters which would give complete signal loss at a specified temperature (chosen as 45°C); they determined the T1 relaxation time at 45°C, and used this to calculate the inversion time required to produce zero signal intensity during a turbo-FLASH sequence. Application of these parameters to image ILP of rabbit liver showed a dark (no signal) band moving away from the fibre-tip during ILP, and representing an isothermal region at 45°C. Because of the temperature gradients achieved during ILP, it can be assumed that beyond this band the temperatures are below 45°C and within it they are above 45°C.

Several histological changes have been proposed as being responsible in part to the observed changes in signal intensity during real time MR imaging of ILP. These include: coagulation of proteins, haemorrhage, changes in tissue perfusion, tissue oedema (Young et al, 1994), alteration in ionisation status of atoms within the tissue, changes in tissue haemoglobin (Farahani et al, 1994) may all be responsible for the complex and varied

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signal intensity changes seen on real time T1 and T2W MR imaging. Therefore the use of T1 and T2 parameters for noninvasive temperature measurement is complex.

Other MR parameters that have been investigated for their temperature sensitivity included diffusion coefficients (Dickinson et al, 1986; LiBihan et al, 1989; Bleier et al, 1991), chemical shift imaging and magnetisation transfer coefficient (Young et al, 1994). In most studies, temperature sensitivity has been evaluated in the range required for hyperthermia treatment but not in monitoring ILP. Bleier et al (1991) evaluated diffusion sensitive echo-planar imaging of ILP in gel phantoms and in vivo rabbit brain with images acquired every two seconds. In diffusion sensitive images of ILP in rabbit brain, heat propagation from the fibre tip was seen clearly as a loss of signal which grew in magnitude and spatial extent while the tissue was irradiated by the laser.

4.7.3.2 Experimental studies: Post ILP MR imaging

T2-weighted sequences investigated by some workers (Anzai et al, 1992; Higuchi et al, 1992; Tracz et al, 1992) have been found to show the necrosis with the best contrast, and this appears as a low signal intensity zone surrounded by a high signal intensity rim. Anzai et al (1992) found the high signal intensity rim to correspond to oedema, which progressed to necrosis by 7 days after ILP of bovine liver. Tracz et al (1992) observed similar features on T2W images of ILP in cat brain, but found that the T1W images showed the lesion weakly with diffuse hyperintensity. The hyperintensity was thought to represent haemoglobin decomposition products with paramagnetic properties.

In a further report by the same group (Tracz et al, 1993) that evaluated the temporal evolution of the ILP lesion in cat brain, showed that necrotic lesion reaches its maximum size at 2 days post ILP, with gradual shrinkage at 5 and 14 days. Contrast-enhanced T1W spin-echo images acquired 30 minutes post ILP were qualitatively similar to T2W images acquired immediately post-irradiation. The hyperintense ring on contrast-enhanced images was thought to represent Gd-DTPA entering the lesion through damaged blood vessels, the latter were determined microscopically to be inside the zone of coagulative necrosis. This suggests that the necrotic lesion immediately after ILP is also underestimated by the enhancing halo.

4.7.3.3 Clinical studies: Dynamic imaging

Real-time MR monitoring of ILP therapy has been reported mainly in brain tumours (Kahn et al, 1994) and liver tumours (Vogl et al, 1995). In all cases, the treatments were performed in whole body magnets and monitored using a 2D FLASH sequence. During therapy, an expanding zone of reduced signal intensity was seen at the fibre tip in the studies reported by Vogl et al (1995). In contrast, Kahn et al (1994) observed a gradually
increasing central zone of high signal intensity with a peripheral area of reduced intensity during therapy.

The lesion size as determined on 2D FLASH scans during laser therapy accounted for 88-100% of total lesion size on the contrast-enhanced T1W images acquired immediately post irradiation in the study reported by Kahn et al (1994). The latter images showed a low signal central zone with a thin peripheral enhancing rim. The diameter of the enhancing rim was assumed to represent the total area of laser-induced necrosis, an observation not supported by histological or cytological examination. In the study reported by Vogl et al (1995), no attempt was made to correlate the changes seen on dynamic imaging with immediate post therapy MR images or delayed contrast-enhanced CT.

4.7.3.4 Clinical studies: Post ILP MR imaging

Follow up MR images in the study reported by Kahn et al (1994) showed a reduction in the diameter of peripherally enhancing rim with contrast enhancement persisting at 1 year. Of the eight patient treated in this study, two patients were reported to have developed recurrence in the margin of the treated zone. The histological correlates of the enhancing rim and the zones of persistent enhancement was not evaluated in this study.

The hepatic tumours treated by Vogl et al (1995) showed hyper-enhancement in the border of the treated zone on contrast-enhanced dynamic turboFLASH sequence. Twenty five (76%) of the 33 treated lesions demonstrated normal signal intensity and contrast enhancement at 4 - 8 weeks after therapy. In the remaining 8 lesions, hyper-enhancement of the surrounding tissue was still evident 6 months after ILP. The therapeutic response rate (on the basis that the lesion size remained static) at 12 months was 44% for tumours < 20mm and 27% for tumours greater than 21mm in mean diameter, with no complete disappearance of a lesion.

Harries (1994) studied five breast cancer patients with MR imaging before and within 5 - 24 h after ILP. This showed a close correlation between the histological extent of laser induced necrosis and the area of reduced enhancement on MR images at 5 h (2 patients) and 24 h (3 patients) post ILP. No attempt was made to correlate residual tumour on histology with MR images nor does it appear that the measurements for the zone of laser induced necrosis were made were in the same plane as that of the MR images. The study does not describe the sequence parameters.
4.8 CLINICAL WORK ON ILP

4.8.1 Breast cancer

Steger et al (1989) were the first group to describe the application of ILP in a patient with breast cancer who had refused all forms of conventional treatment. Three tumour sites were treated with ILP under local anaesthesia and subsequent ultrasound scans were said to show an initial dramatic reduction in tumour volume from approximately 3 cc to 0.5cc within 2 months of ILP. Sadly the patient subsequently developed metastatic and progressive disease. In a further report of four patients, Masters and Bown (1990) showed similar dramatic reduction in tumour volumes in two patients within 14 - 20 days of ILP treatment. In the remaining two patients, histological assessment of the operative specimen (surgery performed several hours to 5 days after ILP) showed small but definite areas of thermal necrosis.

These pilot studies led to further detailed evaluation of the potential application of ILP in the treatment of breast cancer prior to surgical excision (Harries, 1994). ILP was performed using a single bare tip fibre connected to the 805nm semiconductor diode laser. The author noted that the technique was safe with minimal complications which included feeling of warmth, pain; necessitating premature termination of treatment in four patients, minor haemorrhage from the needle puncture site 2 h post treatment, and minor skin burn at the needle entry site in one patient. The skin burn healed by small scar which was excised at surgery.

The laser parameters evaluated were a power of 2 - 3W and an exposure duration of 500 - 750 s, although the effects of varying these parameters in the extent of tissue necrosis were not fully analysed. The author observed similar advantages of using a precharred fibre tips compared to clean fibre tip as that reported by Amin et al (1993a). The histological features of ILP in breast cancer were similar to those reported in the ILP of normal liver by other workers (Matthewson et al, 1987; Amin, 1993) including the zone of "in-situ" tissue fixation similar to the "preserved" zone of hepatocytes seen in experimental studies in rat liver (Amin, 1993). The latter zone was consistently present at 1 day and was also seen in the specimen at 94 days. The temporal changes in the ILP lesion showed granulation tissue at the haemorrhagic rim at 5 days which expanded at 34 - 84 days eventually being replaced with a fibrotic mass with periductal elastosis, endarteritis, and fat necrosis. In the specimens resected at 27 - 94 days after ILP, a foreign body giant cell reaction was also evident.
4.8.2 Hepatic tumours

Percutaneous, ultrasound guided ILP, was first reported by Steger et al (1989); two patients with liver metastases were treated with no immediate or delayed complications. To maximise the chance of ablating the entire lesion, one patient had three consecutive treatments and was disease free at 10 months follow-up. In the second patient, four fibres connected to a 1x4 star coupler were used to deliver laser energy. After treatment the fibres were drawn back 2 cm, and the treatment repeated. US at 10 days post treatment showed 46x56 mm well demarcated lesions and CT at 2 months showed an area of necrosis 5 cm in diameter with well demarcated lesion.

The experience of ILP in the treatment of hepatic tumours has been increasing since then. The "pullback" technique described by Steger et al (1989) has been used by other workers to increase the area of necrosis (Masters et al, 1992; Amin et al, 1993). The series reported by Amin (1993) represents the largest experience on ILP of hepatic tumours which included predominantly colorectal metastases. Of the 93 tumour deposits (31 patients) treated, 51 showed complete necrosis, 32 showed more than 50% necrosis and 19 showed less than 50% necrosis. Complete (grade I) necrosis was seen only in tumours less than 4 cm in diameter. Core biopsies taken from grade I lesions showed necrosis only, with no evidence of tumour, except in 4 cases. In 3 of these 4 cases, edge recurrence was seen at follow up CT scans 4 - 6 months after ILP, and in the remaining case tumour recurrence was found on biopsy only, from the edge of the lesion (3 months after ILP). Survival analysis in this group showed a 1-year survival rate of 85%, and 3-year survival rate of 38% which compared favourably with surgical resection.

8.7.3 Other organs

The technique of ILP has been applied clinically in several solid organ tumours including primary brain tumours (Kahn et al, 1994), benign prostatic tumours (Arai et al, 1995), inoperable pancreatic cancer (Steger et al, 1989; Masters and Bown, 1990) and uterine fibroids (Jourdain et al, 1996). In all studies some reduction in tumour volume has been observed, although the follow up has been relatively short. In addition, most studies have been for palliation purposes, and have therefore lacked detailed histological analysis.
8.8 SUMMARY

Since the introduction of the concept of ILP in 1983 by Bown (Bown, 1983), the technique has been applied clinically in several solid human organs. Much of the earlier experimental studies on the optimal laser and optical fibre parameters required for ILP were performed in normal liver animal studies. Because the effects of ILP are not visible directly, the clinical success of ILP is critically dependent upon imaging techniques that can accurately define the extent of tissue necrosis, but more importantly show accurately the residual untreated tumour which will result in early local recurrence. In most studies, detailed imaging-histological correlation of residual tumour has not been undertaken. The data from experimental studies in normal tissue is useful only in providing imaging-histological correlation for the extent of tissue necrosis but does not provide a measure of the accuracy of imaging techniques in showing residual tumour after ILP.

Clinical studies of ILP in breast cancer have evaluated the optimal laser and optical fibre parameters required for creating safe and predictable laser induced necrosis (Harries, 1994). The preliminary experience in the latter study suggests that MR imaging may be more accurate in defining the extent of tissue necrosis than ultrasonography following ILP in breast cancer, an observation that requires further detailed evaluation in view of the lack of accurate imaging-histopathological mapping undertaken in this study.
SECTION B: MR IMAGING IN THE STAGING OF BREAST CANCER

CHAPTER 5: LOCOREGIONAL STAGING OF PRIMARY BREAST CANCER WITH MR IMAGING

CHAPTER 6: A COMPARISON OF MR IMAGING WITH CONVENTIONAL TRIPLE ASSESSMENT IN THE LOCALLY RECURRENT BREAST CANCER

CHAPTER 7: ASSESSMENT OF RESPONSE TO NEOADJUVANT THERAPY FOR LOCALLY ADVANCED BREAST CANCER
CHAPTER 5:  LOCOREGIONAL STAGING OF PRIMARY BREAST CANCER WITH MR IMAGING

5.1 INTRODUCTION

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5.3 RESULTS

5.4 DISCUSSION

5.5 CONCLUSION

5.6 SUMMARY
5.1 INTRODUCTION

The selection of appropriate treatment for patients with breast carcinoma is determined by accurate assessment of disease stage. Complete locoregional staging should enable an accurate assessment of tumour size, multifocality, the presence of an extensive intraductal component (EIC) and involvement of nipple, pectoralis muscle and axillary nodal metastases. Although conventional triple assessment has a high diagnostic accuracy in the differentiation of benign from malignant breast lesions, it has limitations in the accurate locoregional staging of breast cancer.

The potential role MR imaging in the local staging of breast cancer was first shown by Harms in 1993 (Harms et al, 1993). The authors showed that tumour size on MR imaging correlated closely with histological size (although no actual measurements were detailed in this study) and that MR imaging could show additional clinically and mammographically occult tumour foci. Further studies reported by other workers (Orel et al, 1995; Boetes et al, 1995) supported these observations.

The study detailed in this chapter was started in June 1994 with the aim of identifying the accuracy of MR imaging compared with mammography in the locoregional staging of primary breast cancer diagnosed by conventional triple assessment. This study was designed to evaluate all the parameters required in determining disease extent, which to date have not been fully evaluated by other reported studies. By addressing a homogeneous group of patients with diagnosed breast cancer unlike previous studies, this study also attempts to identify clinical situations where pre-operative MR imaging may provide useful additional information in treatment planning.

5.2 PATIENTS AND METHODS

5.2.1 Patient details

The study was conducted during the period June 1994 to September 1996, and included patients attending the breast clinics at University College Hospital, London, and the Royal Surrey County Hospital, Guildford. All patients with a confirmed diagnosis of breast cancer based on clinical, mammographic and or cytological / core biopsy examination were eligible to participate in the study. A preoperative diagnosis of breast cancer was confirmed by fine needle aspiration cytology in all but nine cases in whom a needle core biopsy was required to confirm the diagnosis. Patients requiring diagnostic surgical biopsies or excision of benign tumours based on preoperative triple assessment were not included in this study. The study was approved by the ethics committees of both University College Hospital, London, and Royal Surrey County Hospital, Guildford.
Ninety patients, median age 49 years old (range, 29 - 80 years old) participated in the study. Of these, 81 patients presented with a clinically palpable breast lump, including one patient with bilateral breast lumps. Of the remaining nine patients, 7 presented with skin/nipple changes of which 2 were suspicious of Paget's disease of the nipple, 1 presented with palpable axillary nodes and blood stained nipple discharge and one patient with a previous history of lobular carcinoma requested bilateral prophylactic mastectomies. This provided 92 breasts for surgical treatment and histological evaluation. The clinical stage based on the classification of American Joint Committee on Cancer (1992) in the 81 patients with palpable lump was T1, <2cm (n = 10), T2, 2-5cm (n = 66), T3, > 5cm (n = 3), T4, infiltrating skin (n = 3).

5.2.2 Mammographic interpretation

All mammograms were assessed by a consultant radiologist (Dr Kate Walmsley) experienced in X-ray mammography with knowledge of the clinical findings only. Mammograms were performed using the Mammomat machine (Mammomat 2, Siemens, Germany). Bilateral craniocaudal and oblique mammograms were performed pre-operatively in all patients. Additional views were taken when necessary. The mammographic findings included a mass (n = 43), mass with associated microcalcifications (n=10), mass with a separate area of microcalcifications (n = 8), microcalcifications only (n=16), asymmetric density (n=3), and normal mammogram (n=12). The median age of the latter group was 46 years (range, 33 - 74).

The following features were recorded; number, site, size (maximum diameter) of the suspicious mass, presence of microcalcifications (type, site and extent), relationship to the nipple and pectoralis major and the axillary region for nodes. Tumours were considered multifocal on mammography when two or more discrete suspicious masses were present. The presence of microcalcification separate from the mass or if microcalcifications were seen in more than 1 quadrant was also considered suspicious for multifocal disease.

5.2.3 Breast MR imaging

5.2.3.1 Technique

All patients were screened for contraindications to having MR imaging (e.g. cardiac pacemaker) prior the examination. An intravenous cannula was inserted into a suitable forearm vein, and connected to a long line flushed with saline. This eliminated the need to move the patient out of the magnet for contrast injection and to retune the coil between sequences. The patient was asked to lie as still as possible during the examination. Cushions were used to ensure optimum patient comfort.
MR imaging was performed using a dedicated receive-only double breast coil (Figure 5.1) on a 1 Tesla scanner (Magneton 42 SP, Siemens, Erlangen, Germany). The coil was positioned to the isocentre of the magnet, and automatically tuned. A transverse (transaxial) T1-weighted 3D FLASH sequence (TR 18msec, TE 7msec, FA 40°, 128x256 matrix, 64 partitions, effective slice thickness 2mm, rectangular field of view 410mm, 4.57 min acquisition time) was made before and after enhancement with Gadolinium diethylenetriamine pentacetic acid (Gd-DTPA) (Magnevist, Schering, United Kingdom) at a dose of 0.1mmol/Kg body weight. Each sequence required approximately 5 minutes to reconstruct the images. The contrast was injected rapidly via a presited intravenous cannula connected to a long line, thus avoiding the need to move the patient in between imaging. Only one post Gd-sequence was performed. Short tau inversion recovery sequence (STIR) (TI 140 ms, TR 2660msec, TE 30msec, FA 140°, 160 x 252 matrix, effective slice thickness 5 mm, slice gap 50%, acquisition time 7.0 minutes) was performed before contrast enhancement and FLASH sequence in all but 8 patients. These were acquired in the transverse plane to include all the breast and the axillary region. The total time for which the patient lay in the scanner was approximately 30 minutes. In all cases, MR imaging was performed within one week after the FNAC or core biopsy.

Figure 5.1: Bilateral receive-only double breast coil
5.2.3.2 Breast MR imaging: Interpretation

All breast MR images were assessed prospectively by a consultant radiologist (Dr M Hall-Craggs) and myself with knowledge only of the cytological diagnosis of cancer. Evaluation of the study was performed visually. The unenhanced and contrast-enhanced images were compared slice by slice for new areas of increased signal intensity.

A lesion was considered suspicious of an invasive cancer if a focally enhancing mass was seen. The number, site, size (maximum diameter), morphologic characteristics (spiculated or regular borders) and enhancement characteristics (homogenous, inhomogenous, rim) of the focally enhancing areas were noted. The presence and extent of diffuse patchy enhancement (defined as areas of enhancement > 3mm which had no specific boundaries to indicate a focal mass) was noted and considered suspicious of ductal carcinoma in-situ (DCIS). Linear enhancement in a duct like pattern was also considered suspicious of DCIS. However when low grade homogenous symmetrical enhancement occurred in both breasts, it was considered to be normal enhancement of breast parenchyma.

Suspected cancers were classified as multifocal if two or more clearly separated suspicious enhancing lesions were seen. Cancers were considered multicentric when the focally enhancing masses were present in two separate quadrants or if there was diffuse patchy enhancement in more than 1 breast quadrant. The relationship of the enhancing mass to the nipple, retroareolar region, skin, pectoralis fascia and muscle was assessed. The enhancement characteristics of the nipple and retroareolar region were noted. These are detailed in the results section.

The axillae were examined for the presence of lymph nodes noting the size, number and enhancement characteristics on the contrast-enhanced T1-weighted images and the signal characteristics on the STIR images. Node appearances were scored as abnormal (likely to be malignant) if the following criteria were met; size >5 mm, higher than soft tissue intensity on STIR images and enhancement with Gd-DTPA.

5.2.4 Primary surgical treatment

The surgical procedures were performed on the basis of clinical and mammographic assessment of disease extent and patient preference (but not MR imaging findings). This included 53 wide local excision (WLE) and 39 mastectomies. Axillary node clearance was performed in 83 of the 92 cancers. In the remaining 9 cancers, axillary dissection was not undertaken in 5 patients who were over 75 years old, in the contralateral asymptomatic breast of the one patient treated by prophylactic mastectomy, and in three patients (presenting with nipple retraction) in whom the pre-operative core biopsy and mammography was suggestive of pure DCIS. Tumours with positive margins on WLE
specimens underwent reexcision (i.e. wider resection or mastectomy) with knowledge of the extent of contrast-enhancement on the preoperative MR imaging.

5.2.5 Histopathological assessment.

Specimens were delivered fresh to the laboratory. The orientation of the mastectomy specimen on the chest wall was obvious from the attached axillary tissue. In cases of WLE specimens, the orientation was indicated by marking its margins with sutures. The specimens were sliced in the transverse plane relative to the patient at 10mm intervals to correspond with the transverse MR images, then pinned on to a cork board and fixed in 10% formalin solution. They were examined for macroscopic disease and photographed to allow comparison with the transverse MR images (Figure 5.2). Tissue was taken from the quadrant that contained the primary tumour, nipple, and retroareolar regions and specimen margins. Further blocks were taken from tissue at least 2cm from the gross outlines of the primary tumour, from the remaining quadrants and areas of interest indicated by review of MR images.

Disease extent was described as unifocal (single focus of tumour with defined borders of any size), multifocal cancer (additional foci of infiltrating carcinoma in the same quadrant as the primary mass) or multicentric (additional foci of in-situ or infiltrating carcinoma in quadrants other than that of the primary tumour).

The microscopic features including tumour size (maximum diameter), type, grade, presence of tumour necrosis and associated DCIS were recorded. Extensive intraductal component (EIC) was defined as the combination of intraductal carcinoma comprising 25% or more of the area defined by the borders of the infiltrating tumour, and intraductal carcinoma in adjacent tissue (either in sections free of the infiltrating tumour or extending clearly beyond the infiltrating margins of the tumour). Also included in this group were tumours that were primarily DCIS with focal or multifocal invasion (Schnitt et al, 1984). DCIS if present as a separate focus from the invasive tumour was measured and its location relative to the index tumour noted.
Figure 5.2: (A) Mastectomy specimen sliced at 10mm intervals in a transverse plane relative to the patient. The top slice shows a 40mm tumour (marked with ink) with adjacent fibrocystic change (curved arrow). Microscopic examination showed a 42mm, G2, invasive ductal carcinoma with DCIS confined to the tumour margins. The breast tissue adjacent to the tumour showed fibrocystic changes. (B) Unenhanced and (C) contrast-enhanced T1W MR images show a 45mm homogeneous enhancing mass (straight arrow) which correlated with the invasive tumour. MR images show a further area of patchy (thin arrows) and focal enhancement (short curved arrow) , findings which correlated with benign fibrocystic changes. Mammogram showed an ill defined mass with microcalcifications measuring 32mm.
5.2.6 Statistical analysis

Linear regression analysis was used to compare the mammographic and MR size of invasive tumours with histopathological analysis.

5.3 RESULTS

The histological type of cancers are summarised in Table 5.1. Table 5.2 shows the correlation between the histological type of the index cancer and the corresponding mammographic appearances.

Table: 5.1: Histological type of cancers (n=90, including 2 bilateral cancers).

<table>
<thead>
<tr>
<th>Histological Type</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive ductal carcinoma plus DCIS</td>
<td>29</td>
</tr>
<tr>
<td>Invasive lobular carcinoma plus DCIS</td>
<td>9</td>
</tr>
<tr>
<td>Mucinous carcinoma</td>
<td>4</td>
</tr>
<tr>
<td>Tubular carcinoma</td>
<td>2</td>
</tr>
<tr>
<td>DCIS</td>
<td></td>
</tr>
<tr>
<td>Comedo type</td>
<td>3</td>
</tr>
<tr>
<td>plus microinvasive foci</td>
<td>3</td>
</tr>
<tr>
<td>Non comedo type</td>
<td>1</td>
</tr>
</tbody>
</table>

The figures in brackets indicate tumours with an extensive intraductal component.
**Table 5.2:** Histological distribution of 92 cancers according to their mammographic appearance

<table>
<thead>
<tr>
<th>mammographic appearance</th>
<th>IDC (n=29)</th>
<th>IDC + DCIS (n=39)</th>
<th>ILC (n=9)</th>
<th>ILC+ DCIS (n=2)</th>
<th>others (n=6)</th>
<th>DCIS (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mass (n=43)</td>
<td>12</td>
<td>22</td>
<td>4</td>
<td>1</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>mass + microcal (n=18)</td>
<td>7</td>
<td>8</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>microcal (n=16)</td>
<td>3</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>asymmetric density (n=3)</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>normal (n=12)</td>
<td>7</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

IDC - invasive ductal carcinoma, ILC - invasive lobular carcinoma, microcal - microcalcifications

At MR imaging, the presence of a focally enhancing mass correlated to invasive carcinoma in all but two patients. In both patients, an additional foci of enhancement suggesting multifocal disease was seen, but correlated with benign fibrocystic changes on histological examination. The presence of diffuse and or linear enhancement correlated to DCIS seen histologically in all but five patients. The latter included diffuse enhancement seen in the symptomatic breast in two patients and in the contralateral asymptomatic breast in three. False positive diffuse enhancement correlated to fibrocystic changes, sclerosing adenosis and atypical epithelial hyperplasia.

The median size of all index invasive tumour (n = 85) on histological examination was 21mm (range 6 - 60). This correlated more accurately with MR imaging (median size 24mm, range, 6 - 60, $r^2=0.93$) than did mammographic measurement (median size 20 mm, range, 0 - 65, $r^2=0.59$) (Figure 5.3). MR imaging showed all invasive lobular cancers, the sizes of which correlated closely with histological measurements. In contrast, mammography was normal in two, and showed an area of asymmetric density in one patient (Table 5.2). In patients with mammographic microcalcifications only, MR imaging accurately defined the tumour margins.
Figure 5.3A: Scatter diagram shows correlation between MR imaging and histological assessment of invasive tumour size (n=85 invasive tumours, including tumours with positive margins).

Figure 5.3B: Scatter diagram shows correlation between mammographic and histological assessment of invasive tumour size (n=85 invasive tumours, including 12 normal mammograms).
The morphologic characteristics of the index enhancing masses included spiculated edges or irregular borders ($n = 70 \ [84\%]$) or well defined borders ($n = 15 \ [16\%]$). In these tumours, the distribution of enhancement was homogenous ($n = 55 \ [65\%]$), peripheral or rim pattern ($n = 12 \ [14\%]$) and had patchy areas of non-enhancement within the main enhancing mass ($n = 18 \ [21\%]$) (Figures 5.4A-F). The area of non-enhancement correlated with spontaneous tumour necrosis, area of tumour fibrosis or mucinous change within the tumour.

*Figure 5.4A:* 45-year-old-female with a palpable lump (A) mediolateral mammogram show an area of asymmetric density in the upper outer quadrant of the right breast (arrowed) (B) Unenhanced and (C) gadolinium-enhanced T1W MR images show a 26mm well defined enhancing mass (arrowed). Histological examination showed a 30mm, G1, invasive ductal carcinoma.
Figure 5.4B: 44-year old female with a palpable lump. Transverse (A) unenhanced and (B) gadolinium-enhanced T1W MR images show a 25mm enhancing mass with few non-enhancing areas within it (arrowed). Histological examination showed a 25mm, G3 invasive ductal carcinoma with areas of necrosis and microcalcifications within it.

Figure 5.4C: 65-year-old female with a palpable lump. Transverse (A) unenhanced and (B) gadolinium-enhanced T1W MR images show a mass with non-homogeneous enhancement. The superior and inferior parts of the tumour enhance intensely (straight arrow, short curved arrow), while the middle part shows patchy enhancement (open curved arrow). Histological examination showed a 54mm mucinous carcinoma.
Figure 5.4D: Transverse (A) unenhanced and (B) gadolinium-enhanced T1W MR images show a 30mm mass with peripheral rim enhancement (straight arrows). (C) Microscopic examination shows a 28mm, G3 invasive ductal carcinoma with central necrosis.
Figure 5.4E: (A) Transverse T1W gadolinium-enhanced MR image show a 55mm irregular enhancing mass extending over two breast quadrants (straight arrows). (B) craniocaudal mammogram show a 40mm well defined mass localised to one breast quadrant (short arrow). Histological examination showed a 60mm, G3 invasive ductal carcinoma with DCIS confined within the margins of the tumour.

Figure 5.4F: (A) Transverse T1W gadolinium-enhanced MR image shows a 20mm enhancing mass (straight arrow). (B) mediolateral mammogram show a 10mm zone of microcalcifications only (short arrows). Histological examination showed a 20mm, G2, invasive ductal carcinoma.
Surgical treatment

The histological distribution of cancers according to their mode of treatment, resection margin involvement and imaging finding is shown in Tables 5.3 and 5.4. Based on triple assessment, 53 cancers were treated by WLE, of which 17 (32%) had positive margins at excision.

Table 5.3: Distribution of 53 cancers treated by WLE, resection margin involvement and imaging findings

<table>
<thead>
<tr>
<th>Histological distribution overall (n=92)</th>
<th>Histological distribution WLE (n=53)</th>
<th>Resection margin involvement (n=17)</th>
<th>Mammography</th>
<th>MR imaging</th>
</tr>
</thead>
<tbody>
<tr>
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<td>40 invasive</td>
<td>DCIS 8</td>
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</tr>
<tr>
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<tr>
<td></td>
<td></td>
<td></td>
<td>multifocal 5</td>
<td>multifocal 2</td>
</tr>
<tr>
<td>Multicentric n = 15 [6]*</td>
<td>5 invasive</td>
<td>ductal 2</td>
<td>normal 2</td>
<td>multicentric 5</td>
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<tr>
<td></td>
<td>-lobular</td>
<td>DCIS 1</td>
<td>unifocal 3</td>
<td></td>
</tr>
<tr>
<td>DCIS 1 quadrant (n=2)</td>
<td>2 DCIS</td>
<td>1 unifocal</td>
<td>unifocal 1</td>
<td></td>
</tr>
<tr>
<td>&gt; 1 quadrant (n=5)</td>
<td></td>
<td></td>
<td>multicentric 1</td>
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* indicates tumours with an extensive intraductal component
Table 5.4: Distribution of cancers treated by mastectomy and imaging findings

<table>
<thead>
<tr>
<th>Histological distribution overall (n=92)</th>
<th>Histological distribution (n=39)</th>
<th>Mammography</th>
<th>MR imaging</th>
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<tr>
<td>Unifocal n = 60 [11]*</td>
<td>20 normal</td>
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<tr>
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<td>4 normal</td>
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<td></td>
</tr>
<tr>
<td>Multicentric n = 15 [6]*</td>
<td>10 normal</td>
<td>2 unifocal</td>
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<tr>
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<td></td>
<td>multicentric 6</td>
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<td></td>
</tr>
<tr>
<td>DCIS</td>
<td>5 unifocal 2</td>
<td>unifocal 3</td>
<td>unifocal 1</td>
</tr>
<tr>
<td>1 quadrant (n=2)</td>
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<td></td>
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<tr>
<td>&gt; 1 quadrant (n=5)</td>
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</table>

* indicates tumours with an extensive intraductal component

Unifocal tumours

MR imaging depicted all unifocal tumours. In two patients an additional enhancing mass was seen, which on histological examination of the mastectomy specimen correlated with benign changes (Figure 5.2). In three unifocal invasive ductal cancers, invasive carcinoma was present at the resection margins of the WLE specimen. In all three cases, MR imaging showed a unifocal tumour whose size measured greater than the mammographic and histological size of the invasive tumour in the primary resected specimen. Further wider excision confirmed residual invasive disease in all three patients.
Multifocal / multicentric tumours

Histological examination of the surgical specimens in 90 patients showed additional tumour foci within the same breast quadrant (multifocal tumours) in 10 (11%) patients and in quadrants other than that of the index tumour (multicentric tumours) in 15 (16%) patients. The index tumour in the 10 patients with multifocal tumours was invasive ductal carcinoma. In each case, a single additional tumour foci was seen which was invasive ductal carcinoma in 6 cases and DCIS in the remaining 4 (non-comedo - 2 cases, comedo - 2 cases). Of the 15 patients with multicentric tumours, the index tumour was invasive ductal in 11 and invasive lobular in 4 cases. The additional tumours in these 15 patients were invasive only in 5 patients, DCIS in 4 patients, and both invasive and DCIS in the remaining 6. The number of additional invasive tumours was one (n = 4), two (n = 3) and diffuse disease (n = 4). The median size of the additional invasive focus on histological examination in all 25 patients was 6mm (range, 4 - 18mm).

Of the ten multifocal tumours, mammography was normal in two patients, unifocal in three and was concordant with histological findings in the remaining five. MR imaging showed the additional tumour foci in six patients only. MR imaging missed tumours included an additional invasive ductal carcinoma measuring 4mm in diameter in two patients and a separate foci of non-comedo DCIS measuring 6 - 8mm in maximum diameter in two patients. In the former two patients, the index tumour had an adjacent extensive intraductal component which was depicted on MR imaging as diffuse patchy enhancement adjacent to the focally enhancing invasive tumour, and thus may have obscured the smaller invasive focus. In all ten patients primary surgical treatment based on clinical and mammographic measurement of index palpable tumour was definitive with adequate clearance.

Of the fifteen multicentric tumours, five were treated by WLE and 10 by primary mastectomy. All five WLE specimens had positive margins. The resection margins showed DCIS in one patient, invasive ductal carcinoma in two and invasive lobular carcinoma in the remaining two. Of these mammography was normal in two patients (including one contralateral palpable cancer) and showed a unifocal tumour in the remaining three. MR imaging depicted multicentric (in greater than one quadrant) invasive carcinoma in all five patients and in two patients showed diffuse patchy enhancement in all quadrants (Figure 5.5). All five patients subsequently underwent mastectomy, and histological examination confirmed multicentric invasive carcinoma of which two were also EIC-positive.
Figure 5.5  42-year-old female with lump in upper outer quadrant of left breast.

(A) Mammography fails to show the palpable tumour. Transverse (B) unenhanced and (C) gadolinium-enhanced T1W MR images show 14 mm enhancing mass at site of palpable tumour (short arrow on C). Also note an additional 9 mm enhancing mass (long thin arrow on C), and diffuse patchy enhancement throughout breast parenchyma. Medial quadrant of contralateral breast also shows ill-defined enhancement (straight arrow).

WLE specimen confirmed 14 mm invasive focus with DCIS present at two margins. Residual disease at mastectomy showed a 10 mm invasive tumour with extensive DCIS.

Multiple needle core biopsies of suspicious area in contralateral breast showed epithelial hyperplasia only.
In the ten primary mastectomy specimens with multicentric cancer, MR imaging of the breast showed all multicentric invasive and in-situ foci. Mammography was normal in two patients (includes one contralateral asymptomatic cancer treated by prophylactic mastectomy), showed a unifocal tumour in two, and was concordant with histological findings in the remaining six patients. Histological examination in the patient treated by prophylactic mastectomies showed multifocal invasive lobular carcinoma in the right breast, and several foci of DCIS and lobular carcinoma in-situ in the both breasts. In this patient, MR imaging showed multiple areas of focal and diffuse enhancement in both breasts. In order to understand this pattern of enhancement further, image subtraction and reregistration was performed using a in-house developed computer software. The subtracted images showed marked linear ductal enhancement in association with discrete focal enhancing nodules within the right breast. The left breast continued to show ill defined areas of patchy enhancement (Figure 5.6). The median size on MR imaging of the additional clinically and mammographically occult invasive focus was 6 mm (range, 4 - 21 mm).

**Figure 5.6:** MR images in the patient (50-years-old) with a previous history of invasive lobular carcinoma detected by mammographic screening which showed a 10mm zone of microcalcifications. Transverse (A) unenhanced and (B) gadolinium-enhanced T1W MR images show focal and diffuse enhancement in both breasts. Subtraction images (C) right reregistered image shows marked linear ductal enhancement with discrete focal enhancing nodules and (D) left reregistered image shows mainly linear enhancement.
Ductal carcinoma in situ

MR imaging depicted all seven cases of purely or predominantly DCIS as areas of diffuse patchy enhancement, the extent of which correlated closely with histological examination. Mammography showed microcalcifications in six patients but tended to underestimate disease extent in all cases (Figure 5.8). Based on mammographic extent of microcalcifications, two patients underwent WLE of whom one had positive margins at excision. Further wider resection based on MR imaging findings confirmed residual DCIS with adequate clearance. Histological examination showed multicentric solid and cribriform-type DCIS with no areas of microinvasion. Diffuse patchy enhancement suggestive of pure DCIS was also seen in one quadrant in three contralateral asymptomatic breasts, where multiple needle core biopsies showed benign proliferative changes only (Figure 5.5).

In addition to the seven patients with purely or predominantly DCIS, 41(48%) of the 85 invasive tumours had an associated intraductal component. This was no more than a 2-3mm and was confined to the invasive tumour margins in 22 tumours. In all cases, MR images showed only a focally enhancing mass. In the remaining 19 tumours, DCIS extended beyond the margins of the invasive tumour and constituted an extensive intraductal component (eleven unifocal, two multifocal and six multicentric tumours). In these tumours, MR imaging showed in addition to the focally enhancing mass, adjacent areas of diffuse or linear enhancement (Figure 5.5, 5.7). The presence of extensive diffuse patchy enhancement adjacent to the focally enhancing mass correlated with the presence of EIC in all but five breasts where the area covered by this form of enhancement correlated to sclerosing adenosis and atypical epithelial hyperplasia. The sensitivity and specificity of MR imaging for the presence of EIC was 81% and 93% respectively. The sensitivity and specificity of mammographic microcalcifications (n = 34 mammograms with microcalcifications) for the presence of EIC was 62% and 74% respectively (Table 5.5). Reexcision was done in eight unifocal EIC-positive tumours treated initially by WLE. Residual disease was not found in any patient.
Table 5.5: Extensive intraductal component: Mammography and Breast MR imaging, and pathological correlation

<table>
<thead>
<tr>
<th></th>
<th>Mammography</th>
<th>Breast MR</th>
</tr>
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<tr>
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<td>64</td>
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<td>5</td>
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<tr>
<td>Sensitivity</td>
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<td>81%</td>
</tr>
<tr>
<td>Specificity</td>
<td>74%</td>
<td>93%</td>
</tr>
</tbody>
</table>

Figure 5.7: 57-year-old female with a palpable lump. Transverse (A) Unenhanced and (B) gadolinium-enhanced T1W MR images show a 21mm mass with a peripheral rim enhancement (long curved arrow) and adjacent linear ductal enhancement (short arrow) extending over 10mm beyond the margins of the enhancing mass. Histological examination showed a 20mm invasive lobular carcinoma with an extensive intraductal component.
Figure 5.8: 32-year-old female with a history of blood stained nipple discharge and palpable axillary nodes. (A) Mammography shows scattered microcalcifications (arrowed). Transverse (B) unenhanced and (C) gadolinium-enhanced T1W MR images show diffuse enhancement throughout the breast cone. The enhancing breast tissue borders retromammary fat (long arrow) and extends into retroareolar tissue (short arrow) with a normal nipple. Histological examination at mastectomy confirmed extensive comedo type DCIS with several areas of microinvasion. DCIS was present in the lactiferous sinus but without nipple involvement. The tumour was within 1 mm of the deep resection margin.
Nipple and retroreolar complex

In order to validate the MR appearances of normal nipple-retroareolar complex, a retrospective analysis of 26 histologically proven normal nipple-retroareolar zone in patients treated by primary mastectomy was undertaken. This showed a characteristic "two-layered" appearance to the nipple in 20 cases; a superficial layer of intense linear dermal enhancement (1 - 2 mm thick) with an underlying non-enhancing zone (Figure 5.9 C-D, 5.12). In 4 nipples, minor linear or patchy enhancement was seen in the deeper aspect of the non-enhancing zone (Figure 5.12) and in two nipples, a vertical linear enhancement was seen passing through the non-enhancing zone. The retroareolar tissue showed enhancement equivalent to the rest of the breast parenchyma in all the normal nipples reviewed.

Of the 90 patients in this series, histological examination showed nipple involvement in six cases. These included 5 patients with Paget's disease of the nipple, of which 4 had an underlying multicentric invasive and \textit{in situ} cancer and 1 had pure DCIS. Histological examination in the remaining one patient showed tubular carcinoma localised to the nipple only. The latter patient presented with nipple thickening and a normal mammogram. Wedge biopsy of the nipple showed tubular carcinoma which was completely excised following WLE of the nipple-retroareolar zone.

Mammography was definitive of nipple involvement in one patient only and showed increased retroareolar density with nipple inversion. In the remaining five patients, accurate assessment of nipple involvement was not possible and mammography identified the index tumour in four of the 5 cases only. The MR appearance of the nipple in all five patients with Paget's disease of the nipple showed increased thickening, bulkiness and contrast-enhancement of the entire nipple-retroareolar complex (Figures 5.10, 5.11). In the one patient with tubular carcinoma of the nipple, MR images showed contrast enhancement localised to the nipple only (Figure 5.9).

In four patients treated by primary mastectomy, histological examination showed retroareolar involvement by tumour with nipple sparing (Figure 5.8, 5.12). MR imaging showed increased thickening/bulkiness or a mass in the retroareolar region and a non-enhancing nipple. Of the two cases of false positive diffuse enhancement in the symptomatic breast, one showed enhancement extending into the retroareolar zone. Mammography was able to predict retroareolar involvement in only one of the four cases.
Figure 5.9  52 year-old female presenting with nipple thickening only. Transverse (A) unenhanced and (B) gadolinium-enhanced T1W MR images show nipple enhancement only. Histological examination at WLE showed predominantly tubular carcinoma localised to the nipple. The contralateral normal nipple shows linear dermal enhancement only (C, D).
Figure 5.10: 69 year-old woman presenting with clinical Paget's disease of the nipple. Transverse (A) unenhanced and (B) gadolinium-enhanced T1W MR images shows linear ductal enhancement within the breast parenchyma (open arrow) and extending into the nipple and retroareolar zone (short arrow). Histological examination confirmed Paget's disease of the nipple with extensive comedo type DCIS within the breast.

Figure 5.11: (A) Mediolateral mammogram shows a spiculated mass underneath the nipple. Transverse T1W (B) unenhanced and (C) gadolinium-enhanced MR images show enhancement of entire nipple and retroareolar zone. Histological examination confirmed Paget's disease of the nipple and underlying invasive tumour.
Figure 5.12: Transverse T1W (A) unenhanced and (B) gadolinium-enhanced MR images show diffuse enhancement within the breast cone, which extends into the retroareolar zone. The nipple shows in addition to the linear dermal enhancement seen in B, a further linear strip of enhancement (arrowed) in the deeper aspect of the nonenhancing zone. Histological examination at WLE showed DCIS at two margins. Reexcision by mastectomy showed residual extensive DCIS and a normal nipple.
Axillary lymph nodes

The axillae of 78 of the 92 breast cancers could be assessed on MR imaging (Figures 5.13, 5.14), the reminder being obscured by cardiac flow artefact and / or not included in the field of view (n=6) or due to inadequate MR imaging data(i.e STIR sequence not done) (n=8). MR imaging-histopathological correlation was possible in 75 axillae (a further 3 axillae were excluded from analysis as they were not explored surgically). There was poor correlation between the total number of malignant nodes seen on MR imaging and pathological analysis. The maximum number of nodes identified on MR imaging were five. Using the criteria described in the methods, the sensitivity and specificity of MR imaging in the assessment of the presence of axillary node metastases was 90% and 82% respectively, compared to clinical examination with a sensitivity of 53% (Table 5.6).

Table 5.6: Correlation between clinical assessment and MR imaging assessment of axillary node metastases

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>True positives</td>
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</tr>
<tr>
<td>True negatives</td>
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<td>29</td>
</tr>
<tr>
<td>False positives</td>
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<td>6</td>
</tr>
<tr>
<td>False negatives</td>
<td>19</td>
<td>4</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>53%</td>
<td>90%</td>
</tr>
<tr>
<td>Specificity</td>
<td>46%</td>
<td>82%</td>
</tr>
</tbody>
</table>

This analysis includes the 75 axillae in which MR imaging-pathological correlation was possible.

Figure 5.13 Transverse (A) unenhanced, (B) gadolinium-enhanced T1W, and (C) STIR MR images show 3 enhancing nodes measuring 10mm, 10mm, and 8mm in diameter, with a corresponding high signal on STIR (arrowed). Histological examination showed 5 metastatic lymph nodes(see next page).
Figure 5.13

Figure 5.14: Transverse T1W (A) unenhanced, (B) gadolinium-enhanced and, (C) STIR MR images show one enhancing node measuring 18mm with high signal on STIR (arrowed). Histological examination showed 12 metastatic nodes.
The focus of MR imaging development since the start of this study at our institution has been for staging the extent of disease in patients with a confirmed diagnosis of breast cancer based on triple assessment prior to surgery. In staging applications, high resolution imaging covering the whole breast and preferably the axilla is essential, and while improved specificity is desirable, sensitivity cannot be compromised by reduced spatial resolution and limited coverage as with dynamic imaging techniques. Static contrast-enhanced imaging improves the sensitivity of cancer detection compared with dynamic imaging techniques by enabling the identification of the occasionally slowly enhancing cancers.

An accurate preoperative estimation of tumour size is essential as this would not only guide the surgeon in the extent of primary resection required to achieve microscopically negative resection margins but because it is also an important independent prognostic marker of survival (Carter et al, 1989). The presence of positive resection margins makes accurate pathological measurement of tumour size difficult. The results of the present study are in agreement with other reported studies on the greater accuracy of MR imaging compared to mammography for invasive tumour size measurement (Boetes et al, 1995). In the present series, MR imaging was also more accurate than mammography in the measurement of invasive lobular cancers. This finding is in agreement with some (Rodenko et al, 1996) but not all studies (Kerslake et al, 1995; Boetes et al, 1995) reporting on the accuracy of MR in the measurement of invasive lobular cancer.

Although mammographic microcalcifications are predictive of residual disease after wide local excision or diagnostic biopsies (Walls et al, 1995; Macmillan et al, 1995), they do not guide in the extent of primary resection required to achieve negative margins. The results of the present study show that MR imaging can help define tumour margins in patients with mammographic microcalcifications, finding which may allow a definitive and more accurate resection than the ill defined wider resection recommended with mammographic microcalcifications.

The results of the present study show the improved accuracy of MR imaging compared to mammography in showing additional tumour foci in patients with multifocal and multicentric disease. In the present series, MR imaging identified 21 (84%) of the 25 patients with multifocal and multicentric tumours whereas mammography identified only 11 (44%) patients. All multifocal cancers (additional foci within the same quadrant as the primary) were adequately treated by the first resection based on clinical and mammographic measurements of the primary palpable tumour. As the aim of wide local excision is to excise the palpable or reference lesion with a 1 - 2cm margin of surrounding normal breast tissue, multifocal tumours (additional foci within the same quadrant as the
primary tumour) may be included in the field of resection.

MR imaging would be useful in detecting multicentric disease (additional tumours in quadrants other than that of the primary tumour) as these would be missed even if the resection margins were negative. In the present study, MR imaging accurately identified all five patients with multicentric disease confirmed at mastectomy but who were initially treated by wide local excision and had positive margins. These results are similar to those reported by Orel et al (1995) in a study of 65 patients with breast cancer. In the latter study, 10 patients had additional tumour foci present at an average distance of 4.5cm from the primary tumour and would therefore not have been included in a limited resection of the primary tumour. These results suggest a role for pre-operative MR imaging in patients that are selected for breast conservation surgery based on clinical and mammographic assessment alone.

In a prospective setting, caution needs to be exercised in changing treatment strategy in patients purely on the basis of MR imaging suspected multicentric cancers in view of false positive areas of contrast enhancement. Because certain MR imaging depicted additional foci of enhancement may be clinically and mammographically occult, an MR guided biopsy will be required to ascertain accurately the nature of these lesions before changing the extent of surgical resection. In the present series false positive contrast-enhancement was seen in 7 (7%) of the ninety five breasts (two focally enhancing masses and five breasts with diffuse patchy enhancement). In the series reported by Orel et al (1995) there appears to be an overlap in their interpretation of benign enhancement defined as scattered punctate enhancement measuring 1-2mm in size and enhancement due to additional multifocal disease whose lowest size in some cases was reported as 2mm also. However, at present the exact clinical significance of discovering microscopic multicentric lesions which are otherwise occult on the basis of MR imaging alone in the overall management of patients remains undefined.

In the present series of seven patients with pure or predominantly DCIS, contrast-enhancement was seen on MR imaging as areas of diffuse patchy enhancement that correlated accurately in its extent with histological analysis. Mammographic microcalcifications were seen in six patients but tended to underestimate the extent of DCIS seen histologically such that one patient initially treated by WLE required reexcision. Using similar criterion of diffuse enhancement, Harms et al (1993) were able to depict all seven cases of DCIS in their series of 47 histologically proven cancers whereas Kerslake et al (1995) identified seven of the 13 cases of DCIS where it extended beyond the margins of the invasive tumour. In a series reported by Orel et al (1995) a 6.6cm predominantly intraductal cancer was missed on MR imaging because diffuse enhancement was interpreted as a normal variant of parenchymal enhancement.
Various other morphological patterns of contrast-enhancement have recently been described in patients with pure DCIS (Soderstrom et al, 1996; Orel et al, 1996). In the series reported by Orel et al (1996), MR imaging identified 14 of the 19 cases of pure DCIS as linear enhancement in 10, regional enhancement in 3 and rim enhancement in the remaining one. However, the latter pattern of enhancement is also seen commonly with invasive tumours. Soderstrom et al (1996) reviewed 22 patients, and identified DCIS in all using the 3D RODEO technique. This series included 5 patients with pure DCIS which showed clumped enhancement in 4 cases and linear enhancement in the remaining one. In six patients, DCIS was associated with areas of microinvasion, and in these tumours, the enhancement was spiculated in 3, clumped plus spiculated in 1, and clumped plus linear in the remaining 2 cases. As both studies involved retrospective non-blinded review of MR images, it is not possible to comment on how the various morphological patterns described may be useful in differentiating DCIS from invasive tumours.

In the present series, tumours with a minimal component of DCIS confined within the margins of the invasive tumour showed only a focally enhancing mass on MR images. In the invasive tumours with an extensive intraductal component, MR imaging showed in addition to the focally enhancing mass, adjacent areas of diffuse or linear enhancement. The extent of diffuse enhancement around the focally enhancing mass correlated closely with both the presence (sensitivity 76% and specificity 92%) and extent of EIC compared with mammographic microcalcifications (sensitivity 52% and specificity 88%). In the five false-negative cases (in whom mammographic microcalcifications were also not seen), MR imaging showed only a focally enhancing mass. False-positive diffuse enhancement was seen in five patients where the histology showed atypical epithelial hyperplasia and sclerosing adenosis. Of the benign breast lesions, sclerosing adenosis has been shown to enhance consistently with gadolinium (Harms et al, 1994). The results of our study suggest that the presence of diffuse or linear enhancement on MR imaging of the breast should be further evaluated by MR imaging guided needle biopsy.

Previous MR imaging studies have not fully evaluated its role in the depiction of EIC-positive tumours. Boetes et al (1995) in a subset of eight patients, showed that MR imaging underestimated the extent of EIC by 10mm in all cases, but have not described the differentiating MR imaging appearance of DCIS from invasive tumour. In the study reported by Soderstrom et al (1996), 11 of the 22 patients had an invasive tumour with an associated EIC, and MR images showed spiculated enhancement in 6, spiculated plus ring enhancement in 3, and linear plus clumped enhancement in the remaining 2 cases. It is however not clear as to how the authors have attempted to differentiate the invasive component from DCIS in these cases. In contrast, the criteria used in diagnosing DCIS in our studies have been clearly differentiated from those used in diagnosing an invasive tumour.
The MR imaging features of nipple involvement with tumour or Paget's disease of the nipple have not been fully evaluated previously. Harms et al (1993) in a retrospective analysis noted nipple involvement in two MR images previously interpreted as being a normal enhancement pattern of the nipple-retroareolar complex. Using dynamic MR imaging, Kaiser (1993) showed a rapid initial enhancement of the nipple that exceeded 100% of the unenhanced signal level during the first minute after contrast-material injection in Paget's disease of the nipple. This criterion allowed an accurate diagnosis in four patients, of whom all were missed on mammography. However such observations are not shared by other workers in field of breast MR imaging. In a review article by Weinreb and Newstead (1995), the authors indicate that the nipples are occasionally difficult to identify on MR images and the retroareolar region occasionally enhances intensely.

In the present study, detailed correlation of histologically normal and abnormal nipple with MR imaging shows that accurate distinction between these can be made. The intense enhancement seen in normal nipples is seen as a linear dermal enhancement only with underlying non-enhancing zone. In contrast, pathological nipple involvement shows as increased bulkiness and enhancement of the entire nipple. There were no false positive cases of nipple enhancement in this study. The results of this study also show an improved accuracy of MR imaging compared to mammography and clinical examination in the assessment of the nipple. The mammographic changes associated with Paget's disease of the nipple are non-specific and over 50% of patients with clinically evident disease are reported as having normal mammograms (Ikeda et al, 1993).

The recognition of nipple involvement with tumour pre-operatively is of critical importance in selecting patients that may be unsuitable for breast preservation surgery or nipple preservation mastectomy. The observations in the present study suggest that MR imaging may have a definitive role in the assessment of the nipple-retroareolar complex. This information may enable the safe preservation of the nipple in situations such as centrally placed breast tumours allowing for more cosmetically acceptable results associated with nipple preserving mastectomy.

The accuracy of MR imaging to demonstrate axillary node metastases has not been previously reported. In a subgroup of patients in this series using specific criteria, MR imaging was found to have a sensitivity of 90% and a specificity of 82% in the diagnosis of involved axillary nodes. The criteria used in the diagnosis of metastatic nodes in this series were developed in a non-blinded prospective evaluation of the data. It was observed that enhancing nodes less than 5mm in diameter consistently represented reactive nodes. When enhancing nodes greater than 5mm in diameter and a corresponding high signal node was seen on the STIR images, the sensitivity was 90% and specificity was 82%. In the four false negative cases, no changes were seen in the axilla. It must be
stressed that the criteria used in diagnosing axillary nodal involvement in this study may only be applicable in the symptomatic breast cancer patient. Further experience in screen detected cancers needs to be acquired where different criteria may need to be adopted. The present limitations of axillary MR examination are largely due to the breast coil design which does not optimally cover this region and the associated cardiac flow artefact projected over the axilla during MR imaging of the breast. Although the latter limitation can be improved by scanning the breast with the phase and frequency switched in the appropriate direction, the use of radiofrequency coils specifically designed for axillary imaging will improve the overall accuracy of MR imaging in determining the extent of axillary node disease.

5.6 CONCLUSION

This study has shown that pre-operative MR imaging of the breast can provide additional information of significant clinical benefits in guiding treatment selection for patients with breast cancer diagnosed on the basis of conventional triple assessment. The information obtained from pre-operative MR imaging of the breast can facilitate surgical planning thus reducing the need for repeated excision and patient anxiety.
CHAPTER 6: A COMPARISON OF MR IMAGING WITH CONVENTIONAL TRIPLE ASSESSMENT IN LOCALLY RECURRENT BREAST CANCER

6.1 INTRODUCTION

6.2 PATIENTS AND METHODS

6.3 RESULTS OF PATIENTS WITH PROVEN LOCAL RECURRENCE
  6.3.1 Surgical Treatment With Histopathological Findings
  6.3.2 Mammography
  6.3.3 Breast MR Imaging

6.4 RESULTS OF PATIENTS WITHOUT LOCAL RECURRENCE

6.5 DISCUSSION

6.6 CONCLUSION
6.1 INTRODUCTION

The optimal surveillance method for the early detection of local recurrence following breast conservation treatment remains controversial. The differentiation of recurrent cancer from benign changes attributable to surgical excision and radiation treatment is difficult both on clinical examination and mammography (Sickles and Herzog, 1981; Paulus et al, 1984). Post-treatment mammographic changes are non-specific and may mimic or obscure recurrent tumour (Sickles and Herzog, 1981). Diagnostic problems are also encountered with ultrasonography due to hypoechoic areas and shadowing within scar tissue which are frequently observed (Balu-Maestro et al, 1991). Hence, surgical biopsy based on the results of clinical and mammographic assessment alone have a poor positive predictive value of approximately 50% (Solin et al, 1990; Stomper et al, 1987).

Early reports using contrast enhanced MR imaging to distinguish benign post-treatment changes and recurrent tumours have been promising. The results of these studies are discussed in chapter 2. However, most of these series are small and contain few patients with histologically proven recurrences (Hickman et al, 1994; Kerslake et al, 1994; Murray et al, 1996). Furthermore, patient selection criteria in these studies have not been accurately defined including the exact clinical benefits of MR imaging compared to conventional triple assessment (i.e. clinical, cytology and mammography).

The purpose of this chapter is to compare breast MR imaging and triple assessment for diagnosis and assessing the extent of local tumour recurrence, in patients with a high clinical suspicion of local recurrence following breast conservation surgery, and to define the MR imaging enhancement and morphological characteristics of recurrent breast cancer and post-irradiation fibrosis with detailed histopathological correlation.

6.2 PATIENTS AND METHODS

In our institution, an average of 150 women with newly diagnosed breast cancer are seen each year and breast-conserving treatment is performed in approximately 60% of these cases. In an 18 month interval, thirty patients previously treated by breast-conservation surgery attending the follow-up breast clinic were suspected on clinical examination to have a high suspicion for local recurrence within the treated breast and were included in the present study. The clinical suspicion for local recurrence was based on the presence of a clinically palpable lump in six patients and localised or diffuse thickening within the treated breast in the remaining 24 patients. All except one patient had previously had post-operative radiotherapy. The median interval from original surgery to suspected local recurrence was 52 months (range, 6 - 185). One patient with diffuse thickening of the treated breast also presented with a contralateral palpable lump in the untreated breast.
Initial assessment of the clinically suspicious region included fine needle aspiration cytology (FNAC) in all patients. Malignant cells were detected in 11, suspicious but probably benign in 3 and benign ductal cells only in the remaining 16 patients. Further outpatient histological evaluation was performed by means of needle core (Tru-cut) biopsy under ultrasound guidance in 9 patients. In the one patient with a contralateral breast lump, cytology showed malignant cells.

Bilateral craniocaudal and oblique mammograms were performed in all 30 patients and compared to previous mammograms. Additional views were taken when necessary. The following features were recorded; number, site, size (maximum diameter) of the suspicious mass and presence of microcalcifications (type, site and extent) in comparison to previous mammograms. The clinical site of suspected recurrence was indicated on the request form and all mammograms were assessed by a consultant radiologist (Dr Kate Walmsley) experienced in X-ray mammography.

MR imaging of the breast was performed using the technique detailed in chapter 3. All breast MR images were assessed prospectively by a consultant radiologist (Dr M Hall-Craggs) with knowledge only of the study protocol. Abnormal masses within the breast and their enhancement characteristics were noted. The presence of focal enhancement (defined as an enhancing mass with an edge) and diffuse ill defined enhancement was recorded. The number, site and size (maximum transverse diameter) of the focally enhancing areas were noted. The extent of diffuse patchy enhancement was also measured and skin and breast parenchyma changes were recorded.

Suspected recurrent cancers were classified as unifocal or multifocal (if two or more clearly separate suspicious enhancing lesions were seen or if there was diffuse patchy enhancement in more than one breast quadrant). Following surgical resection, detailed imaging-histopathological correlation was undertaken as described in chapter 3.

6.3 RESULTS OF PATIENTS WITH PROVEN LOCAL RECURRENCE

6.3.1 Surgical treatment and histopathological findings

Table 1 summarises the results of the study. Local recurrence was confirmed histologically in 14 patients with a median age of 52 years (range 34 - 80). The median interval to recurrence was 50 months (range, 6 - 156 months). FNAC of the clinically suspicious region was diagnostic in 11 (78%) of these 14 patients. Pre-surgical diagnosis in the remaining three patients was obtained by ultrasound guided "Tru-cut" biopsy in 2 and surgical excision in 1 patient, in whom ultrasound guided biopsy was not diagnostic.
Table 6.1: Outcome of investigations in suspected local recurrence in 30 patients

<table>
<thead>
<tr>
<th></th>
<th>FNAC</th>
<th>Mammography</th>
<th>Breast MR</th>
</tr>
</thead>
<tbody>
<tr>
<td>True positive</td>
<td>11</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>True negative</td>
<td>16</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>False positive</td>
<td>0</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>False negative</td>
<td>3</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>79%</td>
<td>50%</td>
<td>92%</td>
</tr>
<tr>
<td>Specificity</td>
<td>100%</td>
<td>75%</td>
<td>88%</td>
</tr>
</tbody>
</table>

Definitive surgical treatment of the treated breast comprised wide local re-excision in 6 patients and mastectomy in 8. Patients offered further breast-conservation surgery had initially undergone local surgery (lumpectomy) prior to our current policy of wide local excision or quadrantectomy as primary treatment. Axillary node clearance was performed in 6 patients in whom the axilla had not previously been cleared. This confirmed metastatic nodes in 3 patients. The contralateral lump in the one patient was treated with wide local excision.

Recurrent tumours were localised to the previously treated breast quadrant in all except one patient. The histologic types of recurrent tumour were infiltrating ductal carcinoma (n=11), invasive mucinous carcinoma (n=1), intracystic papillary carcinoma (n=1) and ductal carcinoma in situ (n=1). The recurrent tumour was unifocal in 10, multifocal in 1 and diffuse in 3 patients. Diffuse recurrence was evident on microscopic examination as scattered cancer cells present within a fibrotic stroma. Within 2 of the 3 diffuse recurrences, a single tumour focus measuring 9 and 10mm in diameter, respectively, was seen. Diffuse recurrent tumour was localised to a single quadrant in 1 patient and to two quadrants in 2. The median size of tumour recurrence within the conserved breast was 20mm (range 8-35). Histological examination of contralateral lump showed a 10mm invasive ductal carcinoma.
6.3.2 Mammography

Mammography identified seven (50%) of the 14 histologically proven recurrent tumours in the conserved breast. Serial mammographic examination showed that the area of abnormality was present 12 months prior to diagnosis in 2 of the 7 patients, but had earlier been interpreted as suggestive of post-operative scar tissue rather than recurrent tumour (Figure 6.1). The mammographic appearance of the recurrent tumours was a spiculated mass (n=4) (Figure 6.1) and new microcalcifications (n=3). The mammographic findings in the one patient with ductal carcinoma in situ was microcalcifications only. The median recorded tumour size was 13 mm (range 10-35). Mammography underestimated tumour size in 3 of these 7 patients. Mammographic findings in the 7 patients in whom recurrent tumour was missed included deformed, dense breast (n=4) (Figure 6.2), scarring and benign linear microcalcifications (n=3). Two of these false negative mammograms were technically inadequate, adequate views of tumour recurrence in the axillary tail region were precluded by the firm, fibrosed nature of the breast (Figure 6.3). The sensitivity and specificity of mammographic findings for the presence of local recurrence in the conserved breast was 50% and 75% respectively. Mammography also failed to show the contralateral cancer diagnosed in one patient (Figure 6.2)

6.3.3 Breast MR imaging

Breast MR identified 13 (92%) of the 14 recurrent tumours including the contralateral palpable cancer seen in one patient. Pre-contrast T1-weighted images and STIR images were not on their own diagnostic of recurrent tumour. On the post-contrast images recurrent tumour was seen as an enhancing region of a high signal intensity compared to the adjacent irradiated breast tissue. Of the thirteen MR depicted recurrent tumours, seven demonstrated homogenous enhancement (Figure 6.1), three demonstrated inhomogenous enhancement, two demonstrated a focally enhancing mass with adjacent diffuse enhancement (Figure 6.2) and one demonstrated rim enhancement. In the patient with ductal carcinoma in-situ, MR imaging showed an area of ill defined inhomogeneous enhancement. MR imaging identified both axillary recurrent tumours missed on mammography (Figure 6.3). In one patient, nipple enhancement was seen on retrospective review of the MR images (Figure 6.4). The median size of tumour recurrence was 22 mm (range 9 -35), with a good correlation between the size of the unifocal cancer measured by MR and by histopathology ($r^2=0.98$). The sensitivity and specificity of MR for local recurrence within the conserved breast was 92% and 88% respectively.
Figure 6.1: 52-year-old female with a palpable lump 5 years after right WLE and adjuvant radiotherapy. (A) Mediolateral mammogram 4 years after WLE and adjuvant radiotherapy shows an area of increased density at the operative site and interpreted as scar tissue (arrowed). (B) Follow-up mammogram obtained a year later shows an obvious 20mm spiculated mass at the same position (arrowed). Transverse unenhanced (C) and gadolinium-enhanced MR images show a 20mm spiculated enhancing mass (arrowed). Histological examination following mastectomy showed an 18mm, G 2, invasive ductal carcinoma.
Figure 6.2: 34-year-old female with diffuse thickening of the left breast and a palpable lump in the right breast, 2 years after WLE and adjuvant radiotherapy for left breast cancer. Ultrasound guided biopsies of the left breast were non-diagnostic. (A) Mediolateral mammograms, 1 year after adjuvant radiotherapy show bilateral radiodense breasts, and (B) at 2 year follow up show a smaller left breast with increased parenchymal density. The right breast shows a 3cm well defined oval radiolucent lump in the upper outer quadrant, but not at the site of the clinically palpable lump (arrowed). Transverse gadolinium-enhanced MR images of (C) the right breast show a 10mm unifocal mass with rim enhancement (arrowed), and (D) the left breast shows a unifocal enhancing mass (arrowed) with background diffuse enhancement (short thin arrows). Histological examination at right WLE confirmed a 10mm invasive ductal carcinoma, and at diagnostic left WLE confirmed diffuse recurrent carcinoma. The patient was subsequently treated by total mastectomy.
Figure 6.3: (A) Mediolateral mammogram 6 years after right WLE shows a dense breast with marked distortion. The axillary tail could not be included in the field of imaging. Unenhanced (B) and gadolinium-enhanced (C) MR images show recurrent tumour in the axillary tail (curved arrows).
MR failed to identify 1 histologically proven recurrence in whom mammography was also non-diagnostic. Clinical examination revealed a scar nodule which on cytology showed malignant cells. Histological examination showed diffuse scattered cancer cells within a dense fibrotic stroma with no discrete tumour focus.

Breast MR showed the presence of enhancing nodes in the ipsilateral axilla in 3 patients, and in the contralateral axilla in one patient (Figure 6.5). These were interpreted as being metastatic according to the criteria detailed in chapter 3, and correlated accurately with histological examination. The enhancing node in the contralateral axilla was not clinically palpable at the time of MR imaging. At three months follow-up, the latter axillary node was clinically palpable and biopsy confirmed metastatic lymph node.

![Figure 6.4: Unenhanced (A) and gadolinium-enhanced (B) MR images 5 years after right WLE and adjuvant radiotherapy showing recurrent tumour in the treated breast (arrowed) with nipple enhancement (noted at retrospective examination) and a contralateral enhancing axillary node. Histological examination following right mastectomy showed a 20mm invasive ductal carcinoma with pagetoid spread into the nipple. The left axillary node was nonpalpable at the time of MR examination. Biopsy of the palpable node 3 months later confirmed node metastases.](image)
6.4  PATIENTS WITHOUT LOCAL RECURRENCE

Local recurrence was excluded in 16 patients with a median age of 62 years (range 47 - 79). FNAC of the clinically suspicious region confirmed benign ductal cells in all patients. Further histological confirmation was obtained in patients with features suggestive of tumour recurrence on both mammography and MR. This included 2 patients with suspicious MR and mammography and 2 with suspicious mammography only. In addition ultrasound-guided core biopsy was also performed in 3 patients with an abnormal non-enhancing mass on MR images which confirmed radiation fibrosis. In the remaining 9 patients with benign cytology and with no mammographic or MR evidence of local recurrence, further histological diagnosis was not obtained and the median follow up for this group is 12 months (range, 6 - 15).

Contrast-enhancement suggestive of tumour recurrence was seen on MR images in 2 of the 4 patients with suspicious mammographic findings (Figure 6.6). In view of this, a diagnostic wide local excision was performed in these 2 patients which showed intense areas of inflammation and post-radiation fibrosis on histology. The interval from initial surgery in these patients was 28 and 54 months, but both previously had a surgical biopsy for possible local recurrence 12 months prior to MR imaging.

Stereotactic guided core biopsy in the other 2 patients confirmed post-radiation fibrosis. Other benign post-treatment changes seen on MR imaging included linear low signal intensity non-enhancing scar (n=8), skin thickening (n=11) and increased signal intensity in pectoralis muscle on the STIR images (n=5) due to radiotherapy (Figure 6.7). Post-treatment changes were evident in nearly all mammograms, including breast deformity, skin thickening, benign micro- and macrocalcification and irregular scars.
Figure 6.5: 51-year-old female with diffuse thickening adjacent to site of previous surgery. Diagnostic biopsy performed 12 months prior to presentation showed post-therapy fibrosis. (A) Mediolateral mammogram at 1 year follow-up showed new microcalcifications (arrowed) adjacent to the site of previous surgery. Transverse unenhanced (B) and gadolinium-enhanced (C) MR images show an ovoid enhancing mass within the site of previous surgery. FNAC showed benign cells. Diagnostic WLE showed benign inflammatory changes only.
Figure 6.6: 63-year-old female with a palpable lump at the site of previous surgery. Mammogram showed increased density with microcalcification suggestive of post therapy changes. (A) Gadolinium-enhanced MR image shows a spiculated nonenhancing mass which on ultrasound guided biopsy proved to be post therapy fibrosis. (B) STIR MR images show increased signal intensity in the skin and pectoralis muscle in the treated breast only, findings which correlated with benign post therapy changes.
6.5 DISCUSSION

This study did not evaluate MR imaging as a method of serial routine follow-up of the irradiated, conserved breast but examined its possible benefits as an additional imaging technique in patients with a high clinical suspicion of local recurrence. In this unit, follow-up of patients treated by breast-conservation and post-operative radiotherapy includes annual mammography. Clinical follow-up is conducted more frequently and has been shown in other studies to improve the detection of local recurrence (45% versus 34%) compared to annual mammography (Orel et al., 1992). In a series of seventy-two women with histologically proven local recurrence in the irradiated conserved breast, Orel et al. (1993) noted a statistically significant association between detection with mammography alone as compared to clinical examination and lower tumour size (P = 0.05) and a non-statistically significant trend towards non-invasive histological findings.

In the present study, all except one locally recurrent tumours were readily identified as enhancing lesions on the contrast-enhanced T1W FLASH images without the need for dynamic imaging, fat suppression or subtraction imaging. Visual comparison of the unenhanced and contrast-enhanced images allowed areas of enhancement to be identified readily in all cases in this series. This method allows the anatomical position of the areas of enhancement to be noted precisely and also reduces errors in image interpretation due to patient movement during conventional subtraction techniques. In addition, the extent of local recurrence on MR imaging correlated with histological extent. This experience with the FLASH sequence concurs with that of Heywang et al. (1990, 1993) and our studies in primary breast cancers.

In this series, MR imaging identified an additional three patients with recurrent disease not detected by FNAC, one of whom also had a negative ultrasound-guided biopsy. A negative FNAC result in this clinical setting should be interpreted cautiously and should not preclude further investigation of a suspect or equivocal lesion. Core needle biopsy has a higher diagnostic sensitivity than FNAC and should be used to obtain a non-surgical diagnosis (Liberman et al., 1995b): surgical biopsy is indicated in cases where a high index of suspicion remains.

The limited sensitivity of X-ray mammography in this series is consistent with other studies evaluating the role of mammography in the early detection of local recurrence (Paulus et al., 1984; Stomper et al., 1987; Orel et al., 1992). In this study, mammography used as part of the triple assessment did not contribute any additional information in the diagnosis of local recurrence. Indeed, including MR imaging as part of the triple assessment instead of mammography would have increased the sensitivity for detecting tumour recurrence to 100%.
Although serial mammography relies on changes caused by post operative scarring to either stabilise or decrease with time (Paulus et al, 1984), this lack of specificity can delay early detection and treatment of local recurrence. This was observed in 2 of the 7 recurrent tumours which were repeatedly imaged in this series. In addition mammographic evaluation of the irradiated breast is frequently compromised by difficulty in compressing the fibrosed breast or due to architectural distortion or retraction. In these situations MR imaging is of undoubted benefit.

The size of unifocal tumours measured by MR imaging correlated closely with histopathological measurement. This may be helpful for indicating whether further conservation surgery or mastectomy is the most suitable surgical option for managing the recurrent disease. Previous studies have shown the superiority of MR imaging compared with mammography in the detection of multifocal recurrences (Heywang et al, 1993) findings which concur with the results of the present study.

False negative MR findings in locally recurrent tumours have not been previously reported. The single case missed by MR imaging in this series stresses the need for complementary clinical and cytological evaluation of all patients with suspected recurrence. The possible explanation for the lack of contrast enhancement in this patient may be due to the presence of the recurrent tumour as scattered cancer cells rather than as a tumour mass. False negative MR findings reported in primary breast cancer have been primarily non-invasive cancers. The data in the present series of recurrent tumours is not adequate to make any comments on the role of MR imaging in detecting non-invasive recurrence.

False positive contrast-enhancement seen in two patients in this series may be explained by the inflammatory changes induced by relatively recent surgical biopsies. To improve the MR imaging specificity, dynamic imaging with cut-off points of peak contrast-enhancement ranging from 36 secs to 3 minutes have been suggested which reliably differentiate recurrent tumour from post-radiation fibrosis (Gilles et al, 1993; Kerslake et al, 1994; Mussarakis et al, 1995; Murray et al, 1996). However, these studies suffer from lack of histological confirmation in over half the patients studied and the relatively short follow up in these series making an accurate assessment of the role of dynamic imaging difficult. False positive contrast-enhancement is well recognised in the literature and occurs with both dynamic and non-dynamic MR sequences. In these situations, MR guided biopsy is essential for histological confirmation.
Unenhanced T1W images on their own were not of value in the diagnosis of recurrence or distinguishing between local recurrence and fibrosis. These findings are in agreement with some (Gilles et al, 1993; Kerslake et al, 1994; Dao et al, 1993) but not all recently reported studies (Lewis-Jones et al, 1991). In the latter study, recurrent tumour was depicted as an area of intermediate signal intensity close to that of muscle on T1W images and a higher signal compared to normal glandular or dysplastic breast tissue on T2W images. Using these criteria, the study showed a 100% sensitivity with only two false positive cases. In addition, STIR sequences were no better at differentiating fibrosis from tumour recurrence. These observations concur with Dao et al (1993) but differ from those reported by Weiner et al (1988). High signal intensity changes in the skin and pectoralis major on the STIR sequence correlated with post-irradiation changes and not tumour recurrence. On the STIR images, both suspect lesions and surrounding normal breast tissue may be seen as high signal areas because of their relatively long T2 which makes accurate delineation of the lesion difficult. Further evaluation of true fat suppression techniques is needed to allow better differentiation of lesions from surrounding breast tissue.

Morphological characteristics are not specific for tumour recurrence, as areas of fibrosis, radiation damage and post-lumpectomy cavities may appear as spiculated masses on precontrast T1W images. The absence of contrast-enhancement within these morphologically abnormal areas is confirmatory of the absence of recurrence as illustrated in the present series.

Although MR imaging is not recommended within 18 months of breast conservation with adjuvant radiotherapy and within 6 months of surgery alone due to false positive contrast enhancement (Heywang et al, 1990; Heywang et al, 1993) we were able to diagnose recurrent intracystic papillary carcinoma in one patient 6 months after initial surgery. This showed as a focally enhancing mass at the site of the clinically palpable mass. However, there were 2 false positive contrast-enhancement results in patients who had a surgical biopsy 12 months prior to MR imaging. The results in the present study support the reservations expressed by Heywang et al (1993) and caution the interpretation of MR images obtained within 12 months of initial surgery or radiotherapy. However, a recent study reported by Soderstrom et al (1997), showed that 3D RODEO MR imaging can show residual disease in the early post-operative period. In the latter series, MR imaging accurately showed residual disease in 15 of the 18 patients studied within 10 months after initial surgery.
6.6 CONCLUSIONS

The results of this study show that MR imaging is a useful additional investigation, particularly in patients with a high clinical suspicion of local recurrence following breast-conservation surgery and radiotherapy. False negative cases may occur with MR imaging and stress the need for complimentary evaluation of patients treated with breast conservation therapy. Although the high diagnostic accuracy of MR imaging suggests that it may have the potential to replace conventional mammography in selected patients, this needs to be balanced against its current high cost.
CHAPTER 7: ASSESSMENT OF RESPONSE TO NEOADJUVANT THERAPY FOR LOCALLY ADVANCED BREAST CANCER

7.1 INTRODUCTION

7.2 PATIENTS AND METHODS

7.3 RESULTS
   7.3.1 Histopathological findings
   7.3.2 Mammographic findings
   7.3.3 Breast MR imaging

7.4 DISCUSSION

7.5 CONCLUSIONS
7.1 INTRODUCTION

Primary chemotherapy (neoadjuvant) is the initial treatment of choice for patients with locally advanced breast cancer and has been shown to result in a substantial tumour shrinkage and downstaging in almost 70% of such patients (Hortobagyi, 1994). However, what the optimal sequence of subsequent treatment should be, or whether one or two local treatments are necessary is still controversial.

The requirement for further local treatment is based on the assumption that residual disease is present despite primary chemotherapy. The dilemma in the management of the breast after neoadjuvant treatment is in accurately defining the extent of residual disease so that appropriate surgery may be undertaken if indicated. Although previous studies have shown the possibility of performing breast conservation surgery following neoadjuvant treatment, these have used methods of limited sensitivity in defining the extent of residual disease and also have included in their analyses patients with T2 tumours (Canavese et al, 1989; Bonnadona et al, 1990; Schwartz et al, 1994).

Currently response classification is obtained by clinical palpation, ultrasonography, and X-ray mammography. All these techniques are based on changes in tumour morphology, which may not accurately reflect an early tumour response. A large necrotic tumour might show no volume reduction despite response to therapy or a tumour may present a significant reduction in volume in some areas, whereas a selective tumour area might not respond to chemotherapy.

This chapter is aimed at demonstrating the extent of residual disease in mastectomy specimens of patients with locally advanced breast cancer (T3-4, N1-2, M0) treated by primary (neoadjuvant) chemo- and or radiotherapy. The extent and distribution of residual disease at histopathological examination was compared with findings at magnetic resonance (MR) imaging and mammography.

7.2 PATIENTS AND METHODS

Over a period of 1 year, 15 patients with a median age of 50 years (range, 28 - 55) presented with locally advanced breast cancer (T3-4, N1-2, M0) and were prospectively evaluated. Of these nine patients were pre-menopausal and six were post-menopausal. There were 14 unilateral and one bilateral cancer. All patients received neoadjuvant chemotherapy comprising six cycles of CMF (cyclophosphamide, methotrexate, 5-fluorouracil) at a dose of 600, 40, and 600 mg/m^2 respectively on days 1 and 8, with a cycle length of 21 days. Radiotherapy was given to 10 of the 15 patients, at the end of the last cycle of chemotherapy at a total dose of 50 Gy given in 25 fractions. Radiotherapy was limited to the breast, internal mammary nodes and the supraclavicular region.
The median tumour diameter at the start of treatment was 6cm (range 5 -10) with all patients having palpable axillary lymph nodes. Pre-treatment mammography and fine needle aspiration cytology was performed in all patients. In addition "Tru-cut" tissue biopsy was carried out in 7 patients and oestrogen receptor status evaluated. Following the final chemotherapy cycle or radiotherapy session, all patients were evaluated both clinically and mammographically. MR imaging was also performed in 3 patients at the start of treatment and in 8 patients post treatment. The technique and interpretation of MR imaging of the breast was similar to that detailed in chapter 3.

Complete staging in the form of chest X-ray, liver ultrasound and bone scan were performed in all patients at the beginning and end of the neoadjuvant treatment. Patients with distant metastases were excluded from the study.

Following neoadjuvant treatment, patients were jointly assessed by a surgeon and clinical oncologist. All patients were fully informed and consented to mastectomy with full axillary node clearance. Following resection, the specimen was delivered fresh to the pathology laboratory. All specimens were carefully analysed by a dedicated breast histopathologist (Dr Ged Cowley).

All mastectomy specimens were evaluated with serial sectioned pathological analysis as described in chapter 3. Blocks were taken from the tumour where it was visible macroscopically, or from the presumed site of the tumour which appeared as a greyish mottled area with a rather firm texture.

Random blocks from the breast including all the resection margins were also taken. Sections were cut at 3-4μm, stained with haematoxylin and eosin and mounted using standard techniques. The following histological features were noted: maximum tumour size, presence of a focal mass or a more diffuse pattern, type and grade of the tumour. In situations where no residual tumour was initially identified, further search was undertaken using the mammogram or breast MR images as a guide.

7.3 RESULTS

The results of clinical, mammography, MR imaging and histopathological analysis are summarised in Table 1. In 11 breasts, the tumour boundaries were no longer measurable on clinical examination, although the breast was diffusely indurated at the site of initial tumour. In the other 5 breasts, an ill defined lump was palpable in 1 quadrant.
<table>
<thead>
<tr>
<th>Patient / age</th>
<th>Clinical</th>
<th>Neoadjuvant treatment</th>
<th>Post-treatment mammography</th>
<th>Post-treatment MR</th>
<th>Macroscopic examination</th>
<th>Microscopic examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>ES /28 (Fig 7.2)</td>
<td>30mm palpable lump confined to a single quadrant</td>
<td>C</td>
<td>residual microcalcifications</td>
<td>slight reduction in tumour size: extensive diffuse enhancement in lateral half of breast</td>
<td>40mm firm indurated tumour in outer quadrant</td>
<td>Extensive area of DCIS, no invasive focus, max dimension - 50mm</td>
</tr>
<tr>
<td>FS /31</td>
<td>vague thickening</td>
<td>C + XRT</td>
<td>decreased density and size of spiculated mass (15mm)</td>
<td>not done</td>
<td>no tumour</td>
<td>well circumscribed mass, 13mm, G3, IDC with prominent necrosis</td>
</tr>
<tr>
<td>NP /34</td>
<td>Bilateral cancers: no residual lumps</td>
<td>C + XRT</td>
<td>not done</td>
<td>not done</td>
<td>Rt &amp; Lt: no tumour</td>
<td>Lt: extensive DCIS with 2 foci of IDC, max diameter difficult to assess - 20mm Rt: pagetoid spread of tumour within ducts, no invasive tumour seen on initial sampling. Further sampling showed 6mm invasive cancer under the nipple</td>
</tr>
<tr>
<td>MCo /36</td>
<td>no residual lump</td>
<td>C + XRT</td>
<td>decreased area of density + microcalcifications (1 quadrant)</td>
<td>no contrast-enhancement, no evidence of residual tumour</td>
<td>no tumour, extensive fibrosis</td>
<td>scattered degenerate cancer cells, maximum diameter-6mm</td>
</tr>
<tr>
<td>RG /39</td>
<td>vague thickening</td>
<td>C +XRT</td>
<td>decreased size of spiculated mass (25mm)</td>
<td>not done</td>
<td>20mm central firm grey area</td>
<td>2 foci of invasive cancer with DCIS separated by areas of fibrosis and necrosis, maximum diameter-18mm</td>
</tr>
<tr>
<td>RP /47</td>
<td>40mm central residual lump</td>
<td>C</td>
<td>40mm spiculated mass, no change in mammographic size</td>
<td>not done</td>
<td>60mm firm tumour</td>
<td>65mm, G3, IDC, with multiple areas of intratumoural necrosis, node+ve</td>
</tr>
<tr>
<td>Patient</td>
<td>Description</td>
<td>Treatment</td>
<td>Findings</td>
<td>Additional Details</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>MCr/49</td>
<td>no lump</td>
<td>C + XRT</td>
<td>30mm area of microcalcifications (no change in mammographic size)</td>
<td>not done</td>
<td>central greyish mottled area</td>
<td>fibrous tissue infiltrated by adenocarcinoma cells in cords and small groups: maximum diameter-17mm, G2, node+ve</td>
</tr>
<tr>
<td>TB/50</td>
<td>vague thickening</td>
<td>C + XRT</td>
<td>indeterminate mammogram (pre- and post-treatment)</td>
<td>10mm focal enhancing mass</td>
<td>no tumour, mottled yellow-brown indurated area</td>
<td>8mm, G2, IDC, node+ve</td>
</tr>
<tr>
<td>MCl/50</td>
<td>vague thickening</td>
<td>C + XRT</td>
<td>decreased mammographic density</td>
<td>diffuse patchy enhancement in 2 quadrants</td>
<td>no tumour</td>
<td>multiple areas of residual DCIS, maximum diameter - 30mm, node+ve</td>
</tr>
<tr>
<td>MH/52</td>
<td>30mm residual lump</td>
<td>C</td>
<td>25mm residual mass + decreased density</td>
<td>18mm central enhancing mass with tenting of pectoralis, node+ve</td>
<td>20mm central tumour</td>
<td>19mm, G2, IDC, tumour extends to deep resection margin, node+ve, 2 supraclavicular nodes</td>
</tr>
<tr>
<td>CH/52</td>
<td>25mm residual lump</td>
<td>C + XRT</td>
<td>decreased mammographic density</td>
<td>not done</td>
<td>20mm firm spiculated area</td>
<td>23mm, G3, IDC, 1node+ve</td>
</tr>
<tr>
<td>JJ/53</td>
<td>30mm central residual lump</td>
<td>C</td>
<td>20mm residual spiculated mass + microcalcifications</td>
<td>25mm focal enhancement, node+ve</td>
<td>30mm grey mottled area</td>
<td>24mm, G2, IDC, node+ve</td>
</tr>
<tr>
<td>FA/53</td>
<td>vague thickening &amp; nodularity</td>
<td>C</td>
<td>indeterminate (pre- and post-treatment)</td>
<td>24mm focal enhancement with background diffuse patchy enhancement</td>
<td>no tumour</td>
<td>20mm, G2, IDC, with associated DCIS, node+ve</td>
</tr>
<tr>
<td>MJ/54</td>
<td>vague thickening</td>
<td>C + XRT</td>
<td>indeterminate mammogram (pre- and post-treatment)</td>
<td>multiple areas of focal enhancement</td>
<td>50mm firm grey mottled area</td>
<td>40mm, multifocal IDC cancer, additional areas identified by MR correlation</td>
</tr>
<tr>
<td>CM/55</td>
<td>vague thickening and induration</td>
<td>C + XRT</td>
<td>20mm spiculated mass with microcalcifications (no change in mammographic size)</td>
<td>not done</td>
<td>no tumour</td>
<td>45mm, diffusely infiltrating IDC, within areas areas of extensive fibrosis and radiation change</td>
</tr>
</tbody>
</table>

C: chemotherapy; XRT: radiotherapy; IDC: infiltrating ductal carcinoma; DCIS: ductal carcinoma in situ; G - grade
7.3.1 Histopathological findings

Macroscopic examination of the mastectomy slices confirmed visible tumour in 6 breasts only, of which five were clinically palpable. Residual microscopic disease was confirmed in all 16 mastectomy specimens. This was present as a focal mass in 6 specimens and allowed an accurate estimation of the residual tumour diameter. In the other 10 specimens, residual disease was more diffuse and interspersed within areas of normal and necrotic/fibrosed breast parenchyma and extending close to the pre-treatment tumour margins. Accurate estimation of residual tumour size was not possible in these patients, and was taken as the area between positive margins. The median tumour diameter was 2.0cm (range, 0.6 - 6.5). Thus all but two of the tumours were successfully down staged from T3-4 to T2 -T1. Residual tumours were infiltrating ductal carcinoma (n=10), invasive plus ductal carcinoma in-situ (n=4) and pure ductal carcinoma in-situ (n=2). The histological grade of the residual invasive tumour was grade I in 3, grade II in 7 and grade III in 5 patients. Axillary nodes were positive in 7 patients.

In all specimens, extensive chemo-radiotherapy induced fibrosis and tumour necrosis was evident. The median diameter of the residual tumour in the 5 patients treated with chemotherapy only was 24mm (range 19 - 60) and that of patients treated with combined chemotherapy and radiotherapy was 18mm (range 6 - 45). In three of the 11 breasts treated with combined chemotherapy and radiotherapy, the resected specimens had residual tumour less than 10 mm in size. Of these one patient had a 6mm area of scattered cancer cells of doubtful viability. In one patient, on initial tissue sampling, only pagetoid spread of cancer cells within the ducts was noted with no evidence of invasive tumour. However on subsequent histological analysis, a 6mm invasive tumour was detected underneath the nipple. In two patients, residual tumour was completely in-situ with no evidence of invasive foci.

7.3.2 Mammographic findings

Post neoadjuvant mammography illustrated a definite reduction in tumour size in ten of the 16 breasts, although there were no cases of complete mammographic response. Mammography in these 10 patients showed a reduction in the extent of microcalcifications in 3 patients, decreased parenchymal density in 3, and reduction in size of the spiculated mass in the remaining four patients. Of the mammographic features, a residual mass had a closer correlation to histological extent of residual disease.

In the remaining six breasts with no evidence of mammographic response, 3 patients had a normal pre-treatment mammogram. The mammograms in the remaining 3 patients showed no changes in the extent of microcalcifications or the size of spiculated mass following neoadjuvant therapy.
7.3.3 Breast MR imaging

Breast MR imaging had been performed in only three patients at the start of treatment. This showed a large enhancing mass with enhancing axillary lymph nodes consistent with locally advanced breast cancer (Figure 7.1 & 7.2). Post-treatment MR scans were performed in 8 patients. This showed diffuse enhancement in two patients, a unifocal enhancing mass in three (Figure 7.1), multifocal in one, combined focal with diffuse enhancement in one (Figure 7.2) and no contrast enhancement in one. In the latter patient, histopathological examination showed a 6mm area of scattered cancer cells of doubtful viability within a fibrous stroma. A focally enhancing mass correlated histologically to an invasive cancer. The presence of diffuse patchy enhancement correlated to ductal carcinoma in-situ. Non-enhancing areas within the main enhancing mass correlated closely to the presence of intratumoral necrosis in all cases. The extent of contrast-enhancement on breast MR imaging correlated closely in all eight cases with the extent of residual tumour seen on histopathological analysis.

Comparison of the pre- and post-treatment MR images was possible in 3 patients only. This showed a definite reduction tumour size in two patients (Figure 7.1) and no significant change in tumour extent in the remaining one patient (Figure 7.2).
Figure 7.1: Gadolinium-enhanced MR images of a 52-year-old female before chemotherapy (A) shows an extensive irregular enhancing mass with skin thickening. There is a superior nonenhancing component to the mass. After six cycles of chemotherapy, MR images show a definite reduction in tumour size now measuring 18mm in maximum diameter. Histology showed a 19mm, G2, invasive ductal carcinoma with 7 positive nodes.

Figure 7.2: Gadolinium-enhanced MR images of a 28 year-old female with T3N1 carcinoma of the right breast before chemotherapy shows (A) an extensive enhancing mass in the lateral half of the breast cone, and after six cycles of chemotherapy show (B) a slight reduction in extent and intensity of contrast-enhancement. The low-signal spot in the skin represents the site of "Tru-Cut" biopsy.
7.4 DISCUSSION

The need for subsequent surgery following neoadjuvant treatment in locally advanced breast cancer is still controversial with opinions ranging from no additional surgery in patients with complete clinical remission to either breast-conservation surgery or total mastectomy with axillary clearance.

This study confirms several important aspects of neoadjuvant treatment. Firstly using conventional chemotherapy nearly all patients can be successfully down staged. Secondly clinical examination is in itself not accurate for estimating the extent of residual disease. This was evident in our study in that 11 of the 16 breasts showed generalised vague thickening with no clinically palpable lump. In addition, in patients with clinically palpable lump, residual disease extended beyond the margins of the palpable lump. Thirdly, compared with mammography, MR imaging provided a more accurate assessment of the extent of residual disease including the presence of intratumoural necrosis. Finally, on microscopic examination residual disease was not always present as a single focus of carcinoma, but rather as islands of viable tumour cells interspersed within fibrous breast stroma, with tumour deposits extending towards the original resection margin. The heterogenous response of the tumour to neoadjuvant treatment stress the need for meticulous histopathological examination to show the presence of residual disease.

Breast cancer is not an encapsulated tumour, and therefore does not shrink centripetally in response to chemotherapy. Thus, although the tumour may be downgraded clinically it may not have been downgraded histologically. Residual microscopic disease may still be present at the original macroscopic margins as was evident in the mastectomy specimens analysed in this study. Other studies have also confirmed that clinical evaluation of response to chemotherapy is less accurate than pathological assessment of response (Feldman et al, 1986).

Accurate estimation of tumour size in the operating room is difficult as the previously firm tumour loses its consistency following destruction of a significant part of the tumour mass or may only be present as scattered islands of degenerate and viable tumour cells. Some workers have therefore suggested marking the original tumour margins at the start of treatment as this would aid in locating the part to be removed (Zurrida et al, 1994). In addition they have suggested the use of frozen section biopsies of the resection margins to check for the presence of microscopic foci of residual cancer. If involved, further excision is advised until the margins are not infiltrated with malignant cells. However, this technique is difficult and time consuming.
Examination of mastectomy specimens in previous retrospective studies suggest that only 23 - 42.5% of patients may have been suitable for breast conservation surgery (Kuske et al, 1993; Singletary et al, 1992; Calais et al; 1993) with residual disease being present in over 90% of specimens examined (Kuske et al, 1993; Kent et al, 1995). Other studies (Zurrida et al, 1994) have reported a much higher breast conservation rate approaching 90% although only a small percentage of patients with locally advanced breast cancer (T3-4) were included. Thus for accurate surgical planning, an imaging technique with a high sensitivity in detecting residual disease is of critical importance.

The results of the present study indicate that although clinical and mammographic appearances change with neoadjuvant treatment in most cases, they do not correlate with the extent of residual disease, findings which are in agreement with recent reports (Helvie et al, 1996; Vinnicombe et al, 1996). Nevertheless, other workers (Pierce et al, 1996) showed that post-treatment mammography is useful in guiding surgical biopsies after chemotherapy. In the latter study, at a median follow up of 3 years, patients that had post-treatment mammography had a lower recurrence rate (0%) compared with those that did not (20%).

The improved sensitivity of breast MR imaging compared to mammography in the loco-regional staging of primary breast cancer has been demonstrated in chapter 3. The results of the present study confirm that static contrast-enhanced MR imaging is also of value in showing the disease extent after neoadjuvant chemo- and or radiotherapy. The static contrast-enhanced FLASH sequence allows complete coverage of the breast and is useful in showing both early and late enhancing tumours including multifocal disease. These findings are in agreement with the recent study reported by Abrahams et al (1996) using 3D RODEO MR imaging (specialised fat suppressed static contrast-enhanced MR imaging) which accurately predicted the extent of residual disease in 30 (97%) of the 31 cases treated by primary mastectomy. In the same series, mammography correlated with MR imaging responses in only 52% of cases.

In the present series, the non-enhancing zones correlated to areas of necrosis or radiation induced fibrosis. As such zones may be present at the start of chemotherapy, it is important to obtain pre-chemotherapy MR images, to allow the changes in tumour enhancement characteristics to be fully appreciated, as the new non-enhancing zones would be indicative of pathological response. However, Knopp et al (1994) used MR pharmacokinetic mapping and documented that the response to chemotherapy coincided with a deceleration of the rate of contrast media enhancement, and that the intensity of contrast-enhancement could remain high due to chemotherapy induced sclerosis.

In theory, the MR imaging correlate of complete pathological response should be a complete absence of suspicious contrast-enhancement. Such a finding was seen in one
patient in our study, but histological examination showed a 6mm area of residual scattered degenerate cancer cells. In the series reported by Abrahams et al (1996), complete pathological response was seen in 2 patients, but the MR imaging findings in these two patients were not explicitly detailed. However, the one false negative case in the latter study that showed no contrast enhancement had on histological examination small residual foci of cancer cells in the breast and the lymphatic spaces. On dynamic MR imaging study reported by Gilles et al (1994b), delayed contrast-enhancement was seen in one patient and was interpreted as a benign finding. Histological examination in this patient showed only a 2mm area of residual invasive tumour.

The spatial resolution available with present MR imaging techniques is unlikely to be able to resolve such microscopic extent of residual disease. It may prove possible that further technological advances in MR imaging will be able to depict such microscopic disease extent. Furthermore, the clinical significance of the above extent of residual disease in the overall management of the patient remains uncertain. Mastectomy would be a therapeutic overkill in this group of patients. Feldman et al (1986) reported no statistically significant disease-free survival difference between women with residual microscopic disease compared with those who have a complete pathological response. However, the small number of patients in the latter study, precludes generalisations about the prognostic significance of a complete pathologic response versus the prognosis of patients with minimal residual disease.

A potential alternative would be to give adjuvant radiotherapy to patients with complete response on MR imaging (with the knowledge that residual disease if present is unlikely to be more than a few millimetres of scattered cancer cells) with the aim of achieving complete pathological response and completely avoiding surgery. The efficacy of such an approach would however need to be worked out in carefully controlled trials. In the remaining group of patients with residual contrast-enhancement on MR imaging, the extent of surgical resection (i.e, mastectomy versus breast conservation) can be accurately planned with the aim of achieving negative resection margins.
7.5 CONCLUSION

In summary, although the limitation of the present study is the relatively few number of patients studied, the detailed imaging-histopathologic correlations undertaken has provided valuable information that has previously been lacking. The results of the present study and review of the recent literature suggest that MR imaging is undoubtedly superior to mammography in the assessment of response to neoadjuvant therapy for locally advanced breast cancer. Thus with presently available conventional neoadjuvant regimes and imaging techniques (in the absence of MR imaging) any surgery less than a total mastectomy may not achieve complete local control. It is likely that with the introduction of more aggressive chemotherapeutic regimes and advances in the techniques of magnetic resonance imaging safe preservation of the breast might be achieved.
SECTION C: MR IMAGING IN THE TREATMENT OF BREAST TUMOURS

CHAPTER 8: SINGLE FIBRE ILP OF BREAST CANCER: MR IMAGING AND HISTOPATHOLOGICAL CORRELATION

CHAPTER 9: MULTIPLE FIBRES ILP OF BREAST CANCER: MR IMAGING AND HISTOPATHOLOGICAL CORRELATION

CHAPTER 10: DYNAMIC MR IMAGING OF LASER THERAPY TO BREAST CANCER

CHAPTER 11: IMAGE GUIDED ILP IN THE TREATMENT OF FIBROADENOMAS.
CHAPTER 8: SINGLE FIBRE ILP OF BREAST CANCER: MR IMAGING AND HISTOPATHOLOGICAL CORRELATION

8.1 INTRODUCTION

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8.4 DISCUSSION

8.5 CONCLUSION
8.1 INTRODUCTION

The application of ILP in primary breast cancer was first described in detail by Harries et al (1994). The authors found that while ultrasound was useful in guiding needle and fibre-tip placement within the tumour and to help predict tumour size at the start of therapy, it was grossly inaccurate for measuring the extent of laser-induced necrosis. The latter findings led to preliminary studies evaluating delayed contrast material-enhanced CT (n=4) and MR imaging (n=5) in showing the effect of ILP in breast cancer. This study suggested that MR imaging may be more accurate for depicting the effect ILP in breast cancer. However, as indicated earlier in chapter 4, several inadequacies in the latter study prevents an accurate assessment of the role of MR imaging in guiding ILP of breast cancer to be made, and therefore require further detailed evaluation.

For ILP to have a clinical role in the treatment of primary breast cancer, an imaging technique is required that provides accurate initial local staging of disease extent and clearly differentiates between treated (necrotic) and residual (viable) tumour after therapy so further treatment can be given to achieve complete tumour ablation. Ideally, thermal changes should be shown in real time and should accurately predict the final extent of necrosis.

The results in chapter 5 have shown the accuracy of contrast-enhanced MR imaging in defining tumour margins. In the present study, the accuracy of MR imaging in showing the therapeutic effects of ILP in primary breast cancer treated with a single precharred optical fibre is evaluated. Detailed comparison has been made between changes seen on post therapy MR imaging and histopathological measurement of the extent of ILP induced necrosis and residual tumour. In addition, the optimal time interval at which post therapy MR imaging accurately depicts the laser induced therapeutic effect was determined.

8.2 PATIENTS AND METHODS

8.2.1 Patient details

Twenty patients (median age 57 yrs, range 34-79) with breast cancer diagnosed by fine needle aspiration cytology of a breast mass were treated by ILP prior to surgical resection. All patients were recruited from a breast clinic for symptomatic patients and all had a palpable tumour. All patients gave written, informed consent for participation in this study which was approved by the hospital ethical committees on human research (University College Hospitals London, and Royal Surrey County Hospital, Guildford).
8.2.2 ILP technique

The laser used in this study was the semiconductor diode laser (Diomed-25, Diomed Cambridge, UK) with a wavelength of 805nm (Figure 8.1). A sterilised, calibrated, single, freshly cleaved silica clad, 400μm diameter fibre with a bare tip was used to deliver laser energy to the tumour. The fibre tip was precharred by placing a small drop of the patient's blood on it and firing the laser briefly at high power as described by Harries et al (1994). The lesion was treated at low power (2 W for 500 sec: 1000J). A single ILP lesion was made in each patient.

The skin at the site of percutaneous needle insertion was infiltrated with 5 - 10mls of local anaesthetic (1% lignocaine) in all cases. Intravenous analgesia (pethidine 50-100mg) was required in 5 patients only. The procedure had to be stopped in 2 patients at 300 and 350 s due to significant pain, which resolved as soon as the laser was switched off. There were no other complications in this study.

Figure 8.1 Diomed diode laser

Figure 8.2 Single fibre in position within the breast
8.2.3 Ultrasonography

The ultrasound scanning was performed by myself or with the assistance of a radiologist (Dr Zahir Amin: Senior Registrar). At the start of treatment, ultrasound of the palpable breast lump (Aloka 650 [7.5MHz breast probe]; Aloka, Tokyo, Japan) was performed and the maximum tumour diameter measured. Using aseptic technique, a 19-gauge needle was inserted percutaneously under ultrasound guidance so that its tip lay within the tumour centre as much as possible. The precharred fibre was passed through the needle so that its bare tip lay 3mm beyond the needle and well within the tumour. The position of the fibre tip relative to the needle tip was ensured by premarking the fibre with an adhesive flag (Figure 8.2).

All treatments were monitored in real time and the maximum extent of thermal changes (seen as an expanding zone of increased echogenicity) measured. The ultrasound characteristics of the tumour were noted immediately after treatment. No further follow-up ultrasound scans were performed.

8.2.4 Breast MR imaging: technique and interpretation

The technique used for breast MR imaging is detailed in chapter 5. All MR images were carefully reviewed by myself and a Consultant Radiologist (Dr MA Hall-Craggs) experienced in MR imaging of the breast. Pre-treatment images were interpreted in a manner similar to that described in chapter 3 on the staging of primary breast cancer.

On the MR images obtained before ILP, the size (maximum transverse diameter) and site of the main enhancing mass was noted. Any additional areas of focal enhancement suggesting multifocal disease were recorded and measured. In addition, the presence of areas of non-enhancement within the main enhancing tumour mass were noted and measured.

MR images obtained after ILP were compared with the images obtained before laser therapy to identify any changes in tumour morphology and enhancement characteristics. New areas of non-enhancement within previously enhancing tumour were considered to represent areas of laser induced necrosis. The maximum transverse diameter of these zones was measured using standard manufacturer’s software on the imaging console. Post-laser MR images were obtained at 4 and 24 h post treatment in the first three patients studied. As no treatment effects were seen in the 4 h scan in these patients, scans of subsequent patients were obtained at a median interval of 48 h post-treatment (range 24 - 96 h).
8.2.5 Surgical treatment

In all cases, surgery was undertaken as planned at the time of diagnosis based on the clinical and mammographic extent of disease. The operation was performed at a median interval of 5 days (range 1-15) after laser treatment. Nine patients underwent wide local excision and twelve had mastectomy. One patient who initially had a wide local excision, subsequently required mastectomy. All patients except one (aged 79 years old) had full axillary node clearance.

8.2.6 Pathological assessment

Histopathologic assessment of the cases presented in this chapter was undertaken by a single pathologist (Dr Andrew Wotherspoon: Senior Registrar). The methodology used is similar to that described in chapter 3 and was originally developed to accurately correlate the areas of laser damage and residual tumour. On macroscopic examination the features noted were the tumour size and extent, and the presence or absence of laser damage with associated charring. The slices were pinned out on cork board and fixed by flotation in 10% formalin solution. Whole mount blocks were taken to include the area of laser damage and all the surgical resection margins. These were embedded in supracassettes (Tissue-Tek, Bayer diagnostics, London, England). Further blocks were taken from areas of interest seen on the MR images. The location of each block was recorded with special note made of the relationship to overlying skin and the nipple, the only landmarks within the pathologic specimens available for correlation with MR images. Sections were cut at 3-4μm, stained with hematoxylin and eosin (H & E) and mounted using standard techniques.

On microscopic examination, the maximum transverse diameter of the laser induced necrosis was measured including its position relative to the tumour (i.e central, eccentric or outside the tumour margins). In patients with central laser necrosis, the size of residual tumour was obtained by subtracting the maximum transverse diameter of the tumour from the diameter of laser necrosis in the same plane. Because of the very irregular margins of breast tumours on both imaging and histological analysis, accurate comparative volume measurements of tumours and presumed necrotic zones could not be made. The residual tumour type, grade, associated DCIS and oestrogen receptor status were evaluated in all patients. The presence of any additional invasive tumours was also recorded.

In two patients, additional staining with diaphorase was undertaken to demonstrate cell viability. This method utilises the reduction of tetrazolinium salts by nicotinamide adenine dinucleotide phosphate (NADP) diaphorase on frozen tissue sections producing a water soluble intense blue granular precipitate called diformazan (Pearse, 1972). The border between blue stained viable and unstained devitalised structures is delineated
sharply permitting an accurate determination of the extent of tissue necrosis.

8.2.7 Statistical analysis

Linear regression analysis was used to compare the ultrasound, MR imaging and histopathological measurements of the primary tumour, laser induced necrosis and residual viable tumour.

8.3 RESULTS

8.3.1 Histopathological findings

In addition to the 20 clinically palpable tumours in the 20 patients, 7 further tumours were detected on histopathological examination. Fifteen patients had single tumours, 4 had two invasive foci in the same breast (only one of which was palpable) and one had bilateral cancer (a single, palpable tumour on one side, which was treated, and 3 non-palpable tumours on the other side which were not treated). Of the 16 breasts with single tumours, 13 were infiltrating ductal carcinomas, 2 lobular carcinomas and 1 mucinous cancer. The multifocal invasive cancers were all infiltrating ductal carcinomas. The presence of extensive DCIS was noted in 3 of the 5 breasts with multifocal cancer, and 1 of the 16 breasts with unifocal tumours.

In the surgical specimens, macroscopically, the laser burn appeared as a white area surrounding a central charred cavity corresponding to the position of the laser fibre. At the periphery of the white zone was a thin hemorrhagic zone (Figure 8.3a). The microscopic features (Figure 8.3b) were consistent and showed three zones. The charred cavity (zone 1) contained necrotic and carbonised debris. This was surrounded by an area of in-situ fixation (zone 2) characterised by morphologically normal cells but with smeared nuclei which had a featureless, hyperchromatic appearance. The cytoplasm of these cells was hypereosinophilic, consistent with the presence of coagulated proteins. Within the hemorrhagic rim (zone 3), the cells showed less severe damage with unsmeared, slightly hyperchromatic nuclei which retained their chromatin pattern and nucleoli. These cells were surrounded by proliferating fibroblasts, blood vessels and extravasted red blood cells. In the last 2 patients studied, diaphorase staining confirmed that cells in all 3 zones seen on the H & E staining of the laser induced lesion were non-viable. The extent of necrosis seen on H & E and diaphorase staining was the same.
Figure 8.3 (a): Macroscopic section of a lumpectomy specimen 48 h after ILP showing the characteristic 3 zones. The central charred cavity is surrounded by a white zone of in-situ heat fixation and a peripheral hemorrhagic zone beyond which is viable tumour. Low power view (original magnification x 2) of the treated tumour (b) shows the central cavity surrounded by a uniformly pink zone with no visible epithelial cells, consistent with coagulative necrosis. The border between the area of laser necrosis (LN) and residual viable tumor (RT) is indicated (arrowhead). The necrosed zone is eccentric and extends into the adipose tissue on one side (straight arrow).
The area of ILP necrosis was completely confined within the tumour margins in 13 patients, extended beyond the margin of the invasive tumour in 5 and missed the tumour in 2. Accurate estimation of the histological size of the primary tumour or the extent of laser induced tumor necrosis was not possible in the 5 patients where the treatment effect extended across the margins of the tumour. For the 22 tumours in which these measurements could be made on the surgical specimen (13 treated with ILP, 2 in which the ILP missed the tumour completely and 7 untreated), the median size of the invasive tumour was 20 mm (range 4-33).

8.3.2 Ultrasonographic findings

Ultrasound guidance enabled the correct positioning of the laser fibre in all cases except 2 where the area of treatment was shown histopathologically to lie outside the tumour and in the mammary fat. The failure to position correctly in these 2 cases may have been related to the indistinct and poorly defined margins of the invasive cancer as seen on ultrasound. Real time ultrasonographic monitoring was undertaken in all patients. After a delay of approximately 100 seconds, a gradually expanding hyperechoic (bright) region appeared around the fibre tip. The margin of the bright zone, however, was irregular and poorly defined. The echogenic area expanded to reach a peak 300-400 s into treatment and remained approximately the same size and shape until the end of therapy. At the cessation of treatment the bright echogenic area gradually died away such that 5 mins after treatment it was indiscernable from the heterogenous pattern of untreated tumor (Figure 8.4). In addition the changes seen on ultrasound were by no means consistent and in some patients (n=2) very little hyperechoic change was seen. There was a poor correlation between the measured maximum hyperechoic zone during treatment and the histologic extent of laser induced necrosis ($r^2=0.30$) (Figure 8.5 A).
Figure 8.4: Ultrasound scan of the breast showing a 18mm tumour. (A) The needle is positioned within the centre of the tumour (arrowed). Images obtained at 150 s (B-C) and 300 s into treatment show an expanding echogenic zone. (D) Two minutes following ILP the whole lesion becomes echogenic with no clear demarcation between treated and untreated zones.
8.3.3 Breast MR imaging

(a) Pre-treatment MR images

Using MR imaging with the FLASH sequence, a focally enhancing mass was seen which correlated with an invasive cancer on the surgical specimen in all cases. In 3 patients, areas of poorly defined, patchy enhancement were seen on the pre-treatment MR images which corresponded histologically to DCIS. MR imaging depicted all palpable tumours and 5 of the 7 additional invasive tumours seen on histological examination. The two missed cancers were additional invasive tumours in 2 patients and were 4mm diameter infiltrating ductal carcinomas. These were obscured on the images by the presence of diffuse patchy enhancement around the main enhancing mass which had been interpreted as DCIS. MR images depicted DCIS in 3 of the patients with multifocal cancers. However, in the 1 patient with a unifocal invasive tumour and associated extensive DCIS, the MR image showed only a unifocal enhancing mass whose size correlated with the combined in-situ and invasive tumour. In 2 patients, the main enhancing mass exhibited a central area of non-enhancement prior to ILP measuring 10 and 8mm in diameter that corresponded to spontaneous tumour necrosis (Figure 8.6A) and mucinous matrix respectively.

The median diameter of the enhancing masses seen was 21 mm (range 8-40). This correlated closely with the histological size of the 9 untreated and the 13 treated tumours evaluable after ILP (tumours in which the zone of laser induced necrosis did not cross the tumour margin, as described above, which showed a median diameter of 20 mm, range 4-33mm). The correlation coefficient was $r^2=0.90$ (Figure 8.5 B).

(b) Post-treatment MR imaging: 3 h and 24 h post therapy

MR scans (STIR and FLASH) performed 4 h after laser therapy in the first 3 patients studied failed to show any change in the tumour. However FLASH scans performed 24 h after treatment in these patients showed focal areas of non-enhancement within the enhancing mass in 2 patients. In the third case, the fibre tip was incorrectly positioned in fat and no effect was seen. This experience changed our protocol for post treatment imaging and in subsequent patients, scans were performed at a median interval of 48 h after laser therapy (range 24 - 96 h).
(c) Post-treatment MR imaging: 24 - 96 h post therapy

In all cases using gadolinium, the area of tumour necrosis was seen as a region of uniform non enhancement with well defined margins. Residual viable tumour was identified as a persistently enhancing region surrounding the area of necrosis. The non enhancing zone was centrally placed within the invasive tumour in 13 patients (Figure 8.6 & 8.8) and eccentric in position in 5 (Figure 8.7). In 2 patients where the fibre was inadvertently positioned outside the tumour, no effect was visible on either the pre- or post contrast-enhanced images.

In one patient there was near complete ablation of the invasive tumour. Surgery was performed 10 days after ILP and microscopic examination of the resected specimen showed an area of elastosis, scarring and necrosis 14mm in diameter consistent with laser therapy and subsequent healing. The only residual tumour was a thin incomplete rim (1mm) of invasive cancer at one margin (Figure 8.9). This was the only patient in whom any changes could be seen after ILP on STIR or pre-contrast FLASH images. The pre-contrast FLASH image showed an area of increased signal intensity measuring 13mm in diameter with a central dark spot measuring 3mm in diameter (Figure 8.9). However, the residual viable tumour was only just seen on the contrast-enhanced images (Figure 8.9).
Figure 8.6: Transverse T1-weighted gadolinium-enhanced MR image of the left breast before ILP (a) shows a 40 mm enhancing mass with an upper 10 mm area of central non-enhancement and (b) 48 h after ILP shows a new additional lower 10 mm area of non-enhancement. (c) Histological examination confirmed the extent of the invasive tumour and its relationship to the overlying skin (S). Within the tumour is an upper area of spontaneous tumour necrosis (open arrows) and an adjacent lower area of laser induced coagulative necrosis (straight arrows). The central laser induced cavity is indicated by a curved arrow. (original magnification x 2)
Figure 8.7: Pre-treatment transverse T1W MR images of the right breast in a 35 year old woman before (a) and after (b) contrast enhancement shows a 19 mm spiculated mass that enhances throughout (curved arrow). MR images performed 72 h after ILP before (c) and after (d) contrast enhancement show a new eccentric area of non enhancement measuring 12 mm (straight arrow) with a residual 8 mm of enhancing viable tumour at the medial margin (curved arrow). Microscopic examination (e) shows the laser induced coagulative necrosis measuring 13 mm (LN), residual invasive tumor measuring 10 mm (RT) and the relationship of the tumour to the nipple (N). The straight arrows indicates the boundary between the laser treated area and residual tumour (original magnification x 2).
Figure 8.8: Pre-treatment transverse T1W MR images of the right breast in a 35 year old woman before (a) and after (b) contrast-enhancement shows multifocal enhancing mass (short arrow) with adjacent linear ductal enhancement extending into the retroareolar zone and the nipple (short white arrow). Post therapy MR images show a new central area of non-enhancement within the inferior enhancing mass consistent with laser induced necrosis (curved arrow).

Figure 8.9: Transverse unenhanced (A) and gadolinium-enhanced (B) T1W MR images through a 14 mm invasive ductal carcinoma of the right breast following ILP. Before enhancement the lesion shows a central 3 mm area of low signal intensity surrounded by a region of relatively high signal. Following contrast, minor enhancement (1 mm) of the lateral margin of the tumor was seen (curved arrow). The appearance corresponded with the histology which showed a 14 mm area of laser necrosis and an incomplete 1 mm area of residual viable tumor on the lateral margin.
The region of non-enhancement on the contrast-enhanced MR scans corresponded to the entire 3 zones of the histopathologically defined laser burn in all cases. The median diameter of the laser induced necrosis on the contrast-enhanced images was 10mm (range, 7-18mm) and that measured on histologic analysis was also 10 mm (range, 5-15mm). MR over estimated the extent of laser necrosis in 8 patients by a median of 1.5mm (range 1-3mm) and underestimated the lesion in 2 patients by 1-2mm. The correlation coefficients (MR versus Histopathologic analysis) for the laser burn diameter and residual tumour size were 0.80 and 0.86 respectively (Figures 8.5 C-D).

![Graph A](image1)

**Figure 8.5:** (A) Correlation between ultrasound and histological assessment of laser induced necrosis. Correlation coefficient $r^2=0.30$ (n=20 ILP treatments, including 2 patients in whom no ultrasound changes were seen during ILP) (B): Correlation between MR and histopathologic assessment of primary tumour size. Correlation coefficient $r^2=0.90$, (n=22 invasive tumours). Histopathological assessment of primary tumour size was possible in 13 of the 18 laser treated tumours, 2 tumours missed during ILP and in a further 7 untreated tumours in these patients.
Figure 8.5:  (C): Correlation between MR and histologic assessment of laser induced necrosis (inclusive of 5 patients in whom the laser necrosis extended beyond the tumour margin). Correlation coefficient $r^2=0.80$ (n=18). (D): Correlation between MR and histological assessment of residual tumour following ILP (excluding patients in whom the fibre was incorrectly placed). Correlation coefficient $r^2=0.86$, (n=18).
8.4 DISCUSSION

The development of ILP as a definitive minimally invasive treatment for breast cancer would require similar patient selection criteria as those applicable to breast-conservation surgery. The clinical success of ILP is thus dependent upon an imaging technique which accurately identifies patients suitable for breast-conservation and also shows the extent of the treatment effect accurately. The laser treatment itself must not interfere with the assessment of prognostic criteria or the choice of any other appropriate therapies such as radiotherapy or chemotherapy.

The results of the present study support the findings discussed in chapter 3 on the accuracy of contrast-enhanced MR imaging in the local staging of primary breast cancer. The size of invasive tumours measured by MR in this series correlated accurately with those measured on histological analysis. With the exception of 2 small invasive tumours masked by intraductal carcinoma, all other invasive and in-situ cancers in this series were accurately visualised by MR imaging. It is critically important to show the full extent of disease prior to ILP treatment so that additional multifocal disease if present is recognised and not missed. These attributes may enable breast MR to aid in the selection of appropriate patients for breast-conservation. Similarly, the same criteria may be used to select patients for minimally invasive therapy using ILP. Multifocal or multicentric disease and the presence of an extensive intraductal component may be a relative contraindication for ILP.

Pre-treatment MR imaging is important to show the enhancement characteristics of the tumour before treatment such that new changes following treatment can be easily recognised. This is particularly so as areas of nonenhancement may pre-exist in the untreated tumour. These areas (seen in 2 patients in the present study) were found to be due to spontaneous tumour necrosis or mucinous matrix. Such a correlation has been demonstrated in MR imaging of experimental breast carcinomas and including some (Revel et al 1986; Stomper et al, 1995) but not all published breast MR imaging series (Orel et al 1995; Kerslake et al, 1995).

In this study, contrast-enhanced MR imaging, performed 24-96 h after ILP accurately showed the extent of laser induced necrosis as a new non-enhancing zone with well defined margins in almost all cases. The residual tumour was seen as an enhancing zone. There was a close correlation between MR imaging and histological analysis of the extent of laser induced necrosis and residual viable tumour following ILP. The greatest mismatch between MR and pathology seen was 3mm. This may partly be explained by an inevitable small error occurring when measuring the lesions and in getting the planes of imaging and sectioning to correspond perfectly.
Although, it was not the aim of the present study to achieve complete tumour destruction, a near complete tumour ablation was seen in one patient. Histological examination of the resected specimen in this patient showed just a 1mm rim of invasive viable tumour at one margin of the area of laser induced coagulative necrosis. Post-therapy MR images performed at 48 hours after ILP accurately showed the residual tumour as an enhancing spot at one margin. However, such minute area of contrast-enhancement would have been better seen using subtraction imaging.

When patients are treated surgically with wide local excision, the palpable lesion is resected, ideally with a margin of over 10mm of macroscopically normal surrounding breast tissue to ensure that the microscopic disease is well clear of the resection margins. The attainment of tumour free resection margins, initially or after re-excision is the most significant predictor of local control after breast conserving treatment with lumpectomy and radiation therapy (Smitt et al, 1995). Thus a similar approach of treating the mass plus a margin of normal tissue will be necessary to reduce the risk of leaving residual disease when treating patients with ILP. If ILP is ever used as a sole initial treatment, it will probably be necessary to perform guided biopsy of the treated margins to confirm disease clearance analogous to bed biopsies performed surgically.

The gross histological features of ILP in breast cancer that were observed in this study were similar to those described by Harries et al (1994). The cells in the zone of "in-situ" fixation may appear to have intact cell membranes but have a smeared nucleus with loss of chromatin material within the nucleolus and hypereosinophilic cytoplasm consistent with coagulated proteins and cell death. Although the haemorrhagic zone contained cells showing microscopic evidence of sublethal damage, we have shown using diaphorase staining that these cells and those present in zone 2 (in-situ fixation) are non-viable. Thus, all three zones seen on macroscopic examination are indicative of histological necrosis. Diaphorase staining to assess tissue viability is particularly important in the assessment of lesions resected immediately after ILP, as these may show only features of patchy congestion on H&E staining (Amin, 1993). However, at 24 h or more after ILP, the boundaries of the ILP induced lesion are similarly defined on H&E staining and histochemical enzyme analysis (Amin, 1993).

The achievement of complete tumour destruction by ILP would result in loss of all tumour tissue that may be necessary for the prognostic stratification of the patient and choice of further adjuvant treatment. Thus it is critically important to obtain all necessary prognostic information as well as a detailed tissue diagnosis prior to complete tumour ablation. There are several prognostic markers currently being assessed in breast cancer management, of which tumour size, type and grade, oestrogen receptors, progesterone receptors and lymph node status are the most important. Pre-treatment MR images are likely to permit accurate estimation of tumour diameter. Cytological grading of fine
needle aspirates has been shown to correlate accurately with histological grade (Robinson et al, 1994). In addition, prognostic information obtained by pre-treatment needle biopsy has been shown to correlate accurately with histopathological findings on resected tumours and is sufficient to guide the use of appropriate adjuvant therapy (Baildam et al, 1989). Axillary lymphadenectomy may be required to determine lymph node status in selected patients, although preliminary experience as shown in chapter 5 suggests that MR imaging may also prove to be of value in axillary staging.

The results of this study confirm the limitations and usefulness of ultrasound in guiding ILP to breast cancer as expressed by Harries et al (1994). Ultrasound guided optical fibre positioning may also prove difficult in situations where the tumour margins are ill defined or the mass poorly visualised by ultrasound and this may have been the explanation for the 2 misdirected treatments in our series. In this study all patients had a palpable breast tumour but this may not be a prerequisite for ILP. As long as the mass can be seen on some form of imaging, treatment will be possible. In view of the failure of ultrasound in 2 of our cases, MR guidance is likely to be better provided robust interventional MR systems can be developed. Further limitations of ultrasound are its dependence on operator's experience and more importantly the inability to correlate the changes seen on ultrasonography to the exact plane on histological examination.

Our results of MR imaging 4 h post-treatment do not support the observations made by Harries et al (1994), who were able to show the treatment effect in 2 patients studied 5 h post-treatment in their small preliminary series. We are unable to explain the discrepancy in these observations. However, our experience agrees with that of Amin et al (1993b) who showed the optimum time for delayed dynamically enhanced CT scans after ILP of hepatic metastases to be 1-4 days, which corresponds well with the time at which experimental ILP lesions reached their maximum size. The treated area within the liver secondaries appears on contrast enhanced CT as a well defined non enhancing zone and is clearly distinguishable from the residual untreated tumour. Harries et al (1994) studied 4 patients with breast cancer using delayed contrast enhanced CT at 24 h post treatment and were able to show a good correlation between the non enhanced zone and histological necrosis. Although contrast-enhanced CT has a high sensitivity in breast cancer diagnosis (Chang et al, 1978), its use has not gained widespread clinical acceptance, probably due to the associated radiation hazard and the relatively large dose of contrast medium required.

The laser and optical parameters used in the present study were similar to those developed by other workers in the treatment of breast cancer and liver metastases (Amin et al, 1993a; Harries et al, 1994). Our results therefore support the observations made by Harries et al (1994) on the safe and predictable diameter of laser induced necrosis that can be produced using a single pre-charred fibre.
8.5 CONCLUSION

The results of this study have shown that contrast-enhanced MR imaging can accurately define the extent of laser-induced necrosis and residual tumour after interstitial laser photocoagulation therapy in breast cancer. The zone of non-enhancement on MR images corresponds to the entire three zones of histopathologically defined laser induced necrosis. The optimal time to perform post-therapy MR images is at least 24 hours after ILP. These findings may enable in planning further ILP treatment with the aim of complete tumour destruction.
CHAPTER 9: MULTIPLE FIBRE ILP IN THE TREATMENT OF BREAST CANCER

9.1 INTRODUCTION

9.2 PATIENTS AND METHODS
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   9.3.2 Histopathological findings
   9.3.3 Pre-treatment MR images
   9.3.4 Post-treatment MR images
   9.3.5 Complications

9.3 RESULTS

9.4 DISCUSSION

9.5 CONCLUSION
9.1 INTRODUCTION

The median diameter of laser induced necrosis when using a single precharred fibre has been observed to be in the range of 10 - 14mm (Harries et al, 1994; Mumtaz et al, 1996). However, this is insufficient to achieve complete tumour ablation including a margin of macroscopically normal tissue as required during surgical wide local excision. Thus, for ILP to have a clinically useful role in the definitive initial treatment of breast cancer, larger areas of thermal necrosis need to be obtained. The method of achieving such results needs to be clinically safe with no additional morbidity. In the present study, a bare fibre-tip rather than a diffuser-tip was used because it has previously been shown that the latter offers no advantage in terms of size of necrosis produced or efficiency of light delivery (Malone et al, 1992; Ripley P, personal communications).

The aim of this study was (a) to determine the clinico-pathological response of the tumour and adjacent normal breast tissue to multiple fibre interstitial laser photocoagulation, and (b) to determine the accuracy of magnetic resonance imaging in the noninvasive assessment of the above response.

9.2 PATIENTS AND METHODS

Ten patients, median age 57 years (range, 42 - 77 years) participated in the study which was approved by the ethical committees of University College Hospitals, London and Royal Surrey County Hospital, Guildford. All patients had a palpable breast lump which was confirmed to be malignant on triple assessment (clinical, cytological and mammographic examination).

At the start of treatment, the tumour was localised and measured by ultrasound (Aloka 650 [7.5 MHz breast probe]; Aloka, Tokyo, Japan). The skin and peritumoural breast tissue was infiltrated with 5 - 10mls of 1% lignocaine. The introducer needles (19-gauge) were then inserted percutaneously into the breast with an attempt to position the needle tips about 1 - 1.5cm apart in the deepest part of the tumour (Figure 9.1). This distance of fibre tip separation has been evaluated in normal ex vivo liver experiments and found to be the most suitable to ensure necrosis of intervening tissue and in maximising the size of thermal induced necrosis (Steger et al, 1992a).
The 805nm wavelength semiconductor diode laser was used and set to deliver a power of 2W for a duration of 500 s (1000 J) down each fibre. The optical fibre parameters used were similar to that detailed in chapter 8. Each fibre was connected to the output ports of a 1x4 star coupler fibre splitter (Diomed-25, Diomed, Cambridge). A single output fibre (0.4mm glass fibre with silica cladding) delivers the laser energy from the diode laser into the fibre splitter which allows equal splitting ratio with minimal loss (approximately 20%) of the input power at the fibre junctions. Intravenous injection of pethidine (50 - 100 mg) and diazepam (5 - 10mg) was given in all cases before starting laser treatment.

Pretherapy MR imaging was performed in nine patients using the technique detailed in chapter 3. In one patient MR imaging was not performed due to the patient's size which did not allow her to fit into the tunnel of the scanner. Post therapy MR imaging was performed in 7 patients only. In the remaining two patients, MR imaging was not performed because of insufficient time between laser therapy and their planned surgical treatment.

Following definitive surgical treatment, the specimens were analysed histopathologically using the technique detailed in chapter 8. Histopathological assessment involved analysis of all sections taken through the tumour from its superior to inferior borders. Each section was then correlated approximately with the corresponding section on the MR scans.
9.3 RESULTS

9.3.1 Clinical observation

The results of the study are summarised in Table 9.1. All patients tolerated the laser procedure satisfactorily with the use of intravenous analgesia and sedation. Immediately post-treatment the lump became clinically more obvious although the increase in ultrasonographic measurement was no more than a few millimetres in all cases. Other immediate post-treatment changes included overlying skin oedema in all cases and skin bruising in four patients. These changes were more marked in patients with small sized breasts compared to a larger size. In one patient the overlying skin became erythematous during treatment which was therefore stopped after 300 s. The peritumoural oedema and skin bruising resolved by one week in the two patients who had their surgical treatments at 7 and 14 days post ILP respectively. In the remaining 8 patients, surgical treatment was performed at a median interval of 4 days (range, 1 - 6 days). In view of the overlying skin oedema and bruising, the tumour margins could not be accurately worked out by the operating surgeon in patients that had their surgical treatment on day 1 after ILP.
Table 9.1: Summary of patient details treated using multiple fibres

<table>
<thead>
<tr>
<th>Patient / age (yrs)</th>
<th>Interval ILP-MR (days)</th>
<th>Interval ILP-surgery (days)</th>
<th>Real-time US (mm)</th>
<th>Pre-treatment MR (mm) + nodes</th>
<th>Post-treatment MR enhancing zone (mm)</th>
<th>Post-treatment MR nonenhancing zone (mm)</th>
<th>Histological laser induced necrosis (mm)</th>
<th>Histology of residual tumour</th>
</tr>
</thead>
<tbody>
<tr>
<td>EB / 77</td>
<td>2</td>
<td>5</td>
<td>12</td>
<td>28 node-ve</td>
<td>8 (medial margin)</td>
<td>22 *</td>
<td>24 (tumour + fat)</td>
<td>4mm, G1 IDC, at medial margin, separate focus of cribriform DCIS, 0/14 nodes</td>
</tr>
<tr>
<td>JC / 55 (Figs 9.3, 9.4)</td>
<td>1</td>
<td>5</td>
<td>21</td>
<td>32 (rim)** node-ve</td>
<td>1 (rim)</td>
<td>33*</td>
<td>32 (tumour)</td>
<td>4 mm IDC, G2 tumour at inferior margin 0 / 30 nodes</td>
</tr>
<tr>
<td>PG / 56</td>
<td>1</td>
<td>5</td>
<td>16</td>
<td>30 1 node</td>
<td>1 (rim)</td>
<td>33*</td>
<td>35 (tumour + extends into muscle)</td>
<td>no residual tumour &quot;in-situ&quot; tumour fixation suggestive of IDC 1 / 12 nodes</td>
</tr>
<tr>
<td>RB / 61 (Fig 9.5)</td>
<td>2</td>
<td>6</td>
<td>18</td>
<td>25 node-ve</td>
<td>3 (medial margin)</td>
<td>22*</td>
<td>25, (tumour + fat)</td>
<td>3mm, G2, IDC, at medial margin, 0 / 11 nodes</td>
</tr>
<tr>
<td>SH / 58</td>
<td>7</td>
<td>14</td>
<td>12</td>
<td>28 (bilobed mass) axilla not visualised</td>
<td>10 (inferior lobe)</td>
<td>18</td>
<td>20 (tumour + fat)</td>
<td>8mm, G3, IDC,+ comedo-DCIS extending beyond its margins, 0 / 19 nodes</td>
</tr>
<tr>
<td>Case</td>
<td>4th</td>
<td>3rd</td>
<td>2nd</td>
<td>1st</td>
<td># of nodes</td>
<td># of contrast-enhanced scan</td>
<td>Tumour size</td>
<td>Tumour grade</td>
</tr>
<tr>
<td>------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>------------</td>
<td>-----------------------------</td>
<td>-------------</td>
<td>--------------</td>
</tr>
<tr>
<td>IN/73</td>
<td>3</td>
<td>4</td>
<td>22</td>
<td>60</td>
<td>4 nodes</td>
<td>no contrast-enhanced scan</td>
<td>*</td>
<td>38 tumour</td>
</tr>
<tr>
<td>CC/42</td>
<td>1</td>
<td>1</td>
<td>18</td>
<td>30</td>
<td>2 nodes</td>
<td>12 (two margins)</td>
<td>22*</td>
<td>24 tumour</td>
</tr>
<tr>
<td>MC/62</td>
<td>-</td>
<td>1</td>
<td>12</td>
<td>14</td>
<td>not done</td>
<td>not done</td>
<td>22 (tumour + fat)</td>
<td>6mm, ILC, 0/11 nodes</td>
</tr>
<tr>
<td>AD/60</td>
<td>-</td>
<td>7</td>
<td>18</td>
<td>not performed in view of patient size</td>
<td>not done</td>
<td>not done</td>
<td>24 (tumour + fat)</td>
<td>no residual tumour, &quot;in-situ&quot; fixation suggestive of IDC, 0/3 nodes</td>
</tr>
<tr>
<td>MQ/52</td>
<td>1</td>
<td>1</td>
<td>15</td>
<td>34</td>
<td>2 nodes</td>
<td>not done</td>
<td>19 (tumour + fat)</td>
<td>21mm, G2, IDC, 2 nodes</td>
</tr>
</tbody>
</table>

IDC: Invasive ductal carcinoma; ILC: invasive lobular carcinoma; G: grade

* Unenhanced scans showed increased signal intensity at the site of laser treatment.

** pre-treatment MR showed rim enhancement (see Figure 9.4).
9.3.2 Histopathological findings

Macroscopic examination showed two types of appearances. In seven specimens a single central charred cavity was seen measuring 1.0 - 1.6 cm in size (Figure 9.2) with an outer peripheral haemorrhagic rim. In the remaining three specimens, four separate zones of cavitation with a charred lining corresponding to the four fibre tips were seen (Figure 9.3). The distance between the cavities on macroscopic examination was greater than 1cm but less than 1.5cm. In all three specimens a single haemorrhagic rim was seen surrounding the zone(s) of cavitation. In the space between the zones(s) of cavitation and the haemorrhagic rim was the white zone similar to that observed in single fibre treatments.

*Figure 9.2:* Macroscopic section of a WLE specimen obtained 4 days after ILP in a breast tumour treated with four fibres showing a single charred cavity with an outer 40x35mm diameter peripheral haemorrhagic rim. Microscopic examination showed central tumour necrosis measuring 38mm in diameter.
The histological features of laser treatment effects on microscopic examination were similar to those seen during single fibre treatments. The cells in the zone between the four separate charred cavities were definitely necrotic (Figure 9.3B). The microscopic extent of laser induced necrosis correlated with the macroscopic measurement of all three zones (charred cavity, white zone and haemorrhagic rim). In tumours excised at day 1 after ILP, the inflammatory response at the margins of the zone of laser necrosis was more florid as compared with tumours excised at 2 or more days after ILP. In the latter group of resected tumours, features of granulation tissue formation characterised by proliferating fibroblasts was evident at the junction of the zone of necrosis and viable tissue. Microscopic examination confirmed complete tumour ablation in two patients, greater than 90% tumour ablation in five patients, and over 50% tumour ablation in the remaining three patients. The histological type of tumour in the eight patients with residual viable tumour was invasive ductal carcinoma in seven; grade I (n = 1), grade II (n = 4), grade III (n = 2) and invasive lobular in one patient. In 2 patients, additional foci of DCIS were seen remote from the index tumour. Axillary node metastases was seen in four patients.

9.3.3 Pre-treatment MR images

A unifocal enhancing mass was seen in the nine patients who had pre-therapy MR imaging. The enhancing mass had irregular or spiculated margins in all but one patient. The latter had well defined edges. The enhancement pattern of the tumour showed rim enhancement with a central non-enhancing zone in one tumour (Figure 9.4A-B), and homogeneous enhancement in the remaining eight tumours (Figure 9.5). The enhancing mass correlated with the index tumour seen on histological examination in all cases. MR imaging did not show the additional foci of DCIS seen in two patients. The axilla was evaluable in seven patients and accurately diagnosed axillary nodal involvement in all cases using the criteria detailed in chapter 3.

9.3.4 Post-treatment MR images

Of the nine patients who had pre-therapy MR images, only seven had post-therapy MR images. The unenhanced MR images showed areas of increased signal intensity in six cases in whom the MR images were obtained within three days of ILP. In the remaining one patient in whom the MR images were performed at 7 days post ILP, no changes were seen on the unenhanced images. Evidence of oedema within the skin and breast parenchyma was also obvious on some of the early post ILP MR images (Figure 9.5). In one patient, increased signal intensity was also seen within the pectoralis muscle, findings
correlated with muscle necrosis confirmed at surgery.

Post-therapy contrast-enhanced MR images were obtained in 6 of the 7 patients only. One patient was reluctant in having Gd-DTPA injection, although she did have a similar injection for her pre-treatment scan. In this patient, the zone of laser-induced necrosis could not accurately be mapped out. In the remaining six patients, contrast-enhanced MR scans showed the zone of laser induced necrosis as a non-enhancing zone, finding which correlated accurately with the histological extent of laser induced necrosis.

The enhancing zone seen on post-treatment MR scans correlated with residual viable tumour in patients imaged at 48 h or more after ILP (Figure 9.5). In two patients imaged at 24 h after ILP, the non-enhancing zone was bordered by a thin (1mm) enhancing rim. In one of these patient, histological examination of the resected specimen at 5 days after ILP showed complete tumour ablation with features of mild inflammatory response and proliferating fibroblasts at the margins of the zone of laser-induced necrosis. In the other patient, histological examination of the resected specimen at 5 days after ILP showed near complete tumour ablation, with residual tumour at medial margins only but on the outer border of the haemorrhagic rim (Figure 9.4C-D). In the remaining circumference of the laser treated zone, a mild inflammatory response with features of early granulation tissue formation was seen. (Figure 9.3).

9.3.5 Complications

The complications seen during this study included one patient with a skin burn. This measured 1cm in diameter, and was excised at the time of definitive surgery. In another patient, a localised disc of pectoralis major measuring 1.5cm had undergone necrosis, and was excised at surgery. In both cases, the patients did not experience any discomfort in the interval to surgery.
Figure 9.3A  (A) Serial sections of WLE specimen obtained 5 days after ILP. The central slices show four separate charred cavities with an outer single peripheral haemorrhagic rim. The area within the haemorrhagic rim measures 32x28mm. The charred cavities correspond to the position of the fibre tips.
Figure 9.3: (B) Microscopic examination shows near complete tumour ablation with residual tumour measuring 4mm at the medial margin (short arrows) (H&E stain, Original magnification x 1). (C) High power view (H&E stain, x10) shows the junction between the residual tumour (RT) and area of laser necrosis (LN).
Figure 9.4: Transverse T1W (A) unenhanced and (B) gadolinium-enhanced MR images from the superior to the inferior margins of the tumour showing a 32mm enhancing tumour with a 27mm central nonenhancing zone (curved arrow). MR images obtained 24 h after ILP show before (C) contrast enhancement an area of increased signal intensity (straight arrows), and (D) after contrast-enhancement show a 33 mm nonenhancing zone slightly greater than the size of the tumour on the pre-treatment images and a peripheral thin enhancing rim (thin arrows) in one section of the tumour. Microscopic examination shows a near complete tumour ablation with residual tumour at one margin only (Figure 9.3).
Figure 9.4 (cont'd)
Figure 9.5: Contrast enhanced MR images of the left breast before ILP (a) shows a 25mm enhancing mass and (b) 48 h after ILP shows the residual tumour clearly as a 3mm enhancing strip at the medial margin. The breast is swollen with skin oedema (curved arrow). Histological examination 6 days after ILP showed near complete tumour ablation with residual tumour seen at the medial margin only.
9.4 DISCUSSION

The results of the present study have shown that multiple fibres can be safely applied in the treatment of malignant breast tumours with minimal morbidity. Although the clinical response to treatment is more marked with the occurrence of oedema within the skin and breast parenchyma, the histological responses are confined as in single fibre treatment. The occurrence of a clinically obvious lump immediately post treatment is indicative that tumour has responded to treatment. The peritumoural oedema and skin bruising tend to resolve with time.

In the present study using four fibres, fibre tip separation of 1 - 1.5cm effectively increased the diameter of laser induced necrosis by a factor of 2 compared with single fibre treatment. These findings are similar to those reported by Steger et al (1992) in the ILP of normal liver. In cases treated in the present study where there was no overlap in the cavitation seen at the fibre tips, the intervening zone of tissue was necrotic with no skip lesions seen. In the study reported by Steger et al (1992), the temperature in the zone between the four fibres was greater than 60°C which is sufficient to cause cell necrosis.

The relatively large size of the tumours included in the present study is the main reason for the low number of complete tumour ablations. In other studies of ILP the size of the tumour has been a limiting factor of achieving complete ablation even when using "pullback" techniques with multiple fibres (Amin et al, 1993b) or with modified fibres such as diffuser tips (Vogl et al, 1995). In the series reported by Amin et al (1993b), 29% of the tumours less than 4cm failed to show complete necrosis on post ILP CT which was thought to be due to difficulty in accurate needle tip placement. The author concluded that there is a much higher chance of achieving complete necrosis, and include a margin of normal liver, when placing 4 needles into a small tumour with a diameter of 2cm or less, then placing 4 needles into a 3 - 4cm diameter tumour.

However, there are potentially other limitations in achieving complete tumour ablation in ILP of malignant breast tumours. It must be recognised that even small tumours may have irregular spiculated margins with intervening areas of normal breast tissue. Thus, although the tumour focus may have a small diameter, a larger area would need to be included to achieve complete tumour ablation. Secondly, some tumour types may have a diffuse microscopic extent, particularly invasive lobular cancers, and may not be effectively covered by even multiple fibres as observed in one case in this study. Thirdly, the presence of associated intraductal cancer which may extend beyond the margins of the invasive tumour and may be occult on mammography and MR imaging, findings that are illustrated in two cases seen in the present series. Finally, it must be recognised that breast cancer is frequently multicentric in its extent.
Pre-therapy MR imaging is essential as detailed in chapter 8. This allows pre-treatment staging and more importantly shows the enhancement characteristics of the tumour as some malignant tumours may show a peripheral enhancement pattern with a central non-enhancing zone. The limitations of MR imaging in showing microscopic foci of DCIS has been discussed previously in chapter 3. However, the exact clinical significance of such additional foci in the overall management of the patient is still uncertain and may not therefore be critical (Vaidya et al, 1996).

In the present study, unenhanced MR images showed areas of increased signal intensity at the site of laser induced necrosis. Such a finding particularly within the nonenhancing zone seen on pre-treatment images may be useful in indicating a therapeutic effect. The contrast-enhanced MR images showed the area of laser induced necrosis as a non-enhancing zone which correlated accurately with the histological extent of necrosis in all cases, findings similar to those observed with single fibre treatments. The residual enhancing zone seen on the post therapy images correlated with residual tumour only in patients imaged at 48 h or more after ILP. In two patients, imaged at 24 h after ILP, a peripheral enhancing rim measuring 1mm was seen. This correlated with an inflammatory response seen at the margins of a completely ablated tumour in one patient, and in the other patient residual viable tumour was seen only at one margin. In both patients surgical resection was undertaken 4 days after post treatment MR scans. The limitation of MR imaging-histological correlation in this study is that surgical resection was not undertaken on the same day as the post-treatment scans. However, it is likely that the histological changes seen on later days after ILP would have been more acute on days 1 -2 immediately after ILP. The results of the present study suggest that by delaying the post therapy MR imaging for at least 48 hours after ILP an accurate assessment of residual tumour may be made. The relatively small number of patients studied on which this assumption is being made stress the need for further studies evaluating the optimal time required for post therapy imaging in tumours treated using multiple fibres.

Difficulties in the interpretation of enhancing rims on post therapy images have been observed by other workers using computed tomography (Amin et al, 1993; Rossi et al, 1996). Amin et al (1993b) observed that an enhancing rim was seen after ILP of large tumour (3 -3.5cm) but not after ILP of small tumours (< 2cm) and its appearance was not time dependent. In the latter series, an enhancing rim on CT was seen at 1 week after treatment of 4 large tumours. In one case this rim increased in size by 2 months, but the patient was not available for biopsy. In another patient, who had chemotherapy after ILP, the rim disappeared by 6 weeks post ILP, and in the remaining 2 patients, biopsies of the rim showed residual tumour in one and liver tissue with inflammatory changes only in the other.
Enhancing rim on post therapy MR images have been reported in experimental studies (Tracz et al, 1993) and clinical studies of ILP in brain tumours (Kahn et al, 1994). In the study reported by Tracz et al (1993) on ILP of normal cat brain, the enhancing rim was thought to represent Gd-DTPA entering the necrotic lesion through damaged blood vessels. The latter zone on microscopic examination was determined to be within the zone of coagulative necrosis. Kahn et al (1994) observed enhancing rim on MR images acquired immediately after ILP of malignant tumours, but did not evaluate the rim by histological or cytological examination. Enhancing rims post therapy may be caused post treatment oedema seen at the margins of the necrotic lesion, neovascularisation or residual tumour.

In the present series, unlike with single fibre treatments, complications were seen in two patients. This included one skin burn and one pectoralis burn. It is likely that with more careful planning of ILP which should involve an assessment of tumour position relative to the skin and underlying muscle, complications can be avoided. Superficial tumours or tumours close the pectoralis muscle may be treated at two or more sessions but using fewer fibres. Alternative methods of positioning the fibre tip within the tumour such that the thermal effect does not reach important structures need to be evaluated.

The healing of large volumes of thermal necrosis as a result of multiple fibre treatment within the breast remains to be determined. In the study reported by Harries (1994) one patient treated with a single fibre underwent surgical excision at 94 days post ILP. In this patient, the area of laser induced necrosis had healed by the formation of a small fibrotic nodule, although it was not detailed in the results if this nodule had any residual tumour or whether it was clinically non-palpable. It is to be expected that the volume of laser induced necrosis in breast would heal by formation of a fibrotic mass as the latter has limited regenerative potential. In contrast necrosis in liver heals with complete regeneration of liver tissue and minimal fibrosis (Steger et al, 1992). In the breast, what is important is that the fibrotic nodule should not be clinically palpable and that imaging should be able to differentiate residual tumour from fibrosis. The accuracy of contrast-enhanced MR imaging in showing residual tumour soon after ILP is well illustrated in this study and in chapter 8 and its ability to differentiate recurrence from fibrosis is detailed in chapter 4 of this thesis.

Long term data on ILP of breast cancer is not yet available as all patients have had definitive surgery soon after ILP treatment. However, follow up data of over 12 months on ILP of liver metastases is available and lessons from these series can be used in improving the clinical outcome of ILP in breast cancer. In the study reported by Amin (1993), of the grade I lesions (complete necrosis), 4 cases had local recurrence (tumour size 3cm, 1.7cm, 3.5cm, 3 cm), in 3 of these patients edge recurrence was seen on follow up CT scans 4 - 6 months after ILP. In the remaining one patient, edge recurrence was
biopsy proven at 3 months. Similar rates of early recurrences have been seen in other liver metastases series and palliation of malignant brain tumours in cases where 100% or grade I necrosis was shown to be achieved (Vogl et al, 1995; Kahn et al, 1994). The exact reasons for such early recurrences may be related to treating just the tumour margins and not having included adjacent normal tissue, treating lesions greater than 2 cm, or possibly biostimulatory effect of laser light at low energy levels at the edge of the necrotic zone. These results once again illustrate that ILP would be effective in achieving complete tumour ablation with an acceptable local recurrence rate only in small sized tumours that are preferably less than 2cm in maximum diameter.

9.5 CONCLUSION

In summary, ILP using multiple fibres can achieve clinically useful diameters of laser induced necrosis in breast tumours. Tumours less than 2cm in size may be effectively ablated with a four fibre system. Post therapy contrast-enhanced MR images need to be performed at least 48 hours after multiple fibre treatment.
CHAPTER 10: DYNAMIC MR IMAGING OF LASER THERAPY TO BREAST CANCER

10.1 INTRODUCTION

10.2 PATIENTS AND METHODS

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  10.3.4 Histopathological correlation
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10.4 DISCUSSION

10.5 CONCLUSION
10.1 INTRODUCTION

A central problem in interstitial laser therapy is that the size and geometry of thermal lesions are difficult to predict due to biological variability (Cheong et al, 1990), fibre tip charring, changing optical and thermal properties of the tissue during treatment (Svaasand et al, 1985) and the variability of blood flow through tissues which allows heat dissipation during treatment (Matthewson et al, 1987). Thus, for ILP to be clinically useful, it needs to be monitored ideally during therapy such that once the desired volume of tissue coagulation is achieved the treatment can be stopped and also prevent unnecessary tissue damage.

The results in chapter 8 and 9 have demonstrated the accuracy of delayed-contrast enhanced MR imaging in showing the extent of thermal necrosis and residual tumour after treatment but do not exploit the capabilities of MR imaging for the dynamic or “real-time” monitoring of ILP. MR imaging has numerous advantages in evaluating the irreversible effects of laser treatment in tissues as discussed in chapter 7. The temperature dependence of MR parameters such as T1 relaxation times and diffusion coefficients (Dickinson et al 1986; LeBihan et al, 1989) make it particularly suitable for the demonstration and monitoring of thermal energy deposition in tissues.

Several experimental studies have evaluated the changes in MR signal during interstitial laser therapy using gel phantoms, ex vivo tissues in water baths, and in vivo normal tissues (Matsumoto et al, 1992a, 1994; Fried et al, 1996; Roberts et al, 1997a). While the aim of these studies have been to optimise the MR sequences used in monitoring ILP, few have correlated the changes in MR signal with histological analysis (Fried et al, 1996; Roberts et al, 1997a). Likewise, clinical studies of ILP performed under MR imaging guidance have lacked histological correlation because these treatments were aimed at palliating inoperable hepatic metastases or brain tumours (Kahn et al, 1994; Vogl et al, 1995; Roberts et al, 1997b).

The aim of this study was to evaluate the spatial and temporal changes in signal intensity during dynamic MR monitoring of ILP to malignant breast tumours and correlate these with detailed histopathological examination of the resected specimen following definitive surgical treatment.

10.2 PATIENTS AND METHODS

Fourteen women, aged 38 - 86 years (median, 64 years) with breast cancer diagnosed by cytological examination after fine needle aspiration of a breast mass, underwent treatment with ILP prior to surgical resection of the tumour. All patients were recruited from a
breast clinic for symptomatic patients, and all had a clinically palpable, unifocal tumour. All patients gave written informed consent for participation in this study, which was approved by the ethical committees for human research at the University College London hospitals, and the Royal Surrey County Hospital, Guildford, England.

The ILP technique used was similar to that detailed in chapters 8 and 9. The diode laser was installed in the operating console room, and the laser light was transmitted to the MR scanner room through 10m fibreoptic cables. The introducer needles (19 gauge) used were MR compatible (Cook, Bjaeverskov, Denmark) and were positioned within the breast tumour under ultrasound guidance. With these needles in place, the patient was transferred into the MR unit, carefully moved onto the scanner couch and asked to lie prone on a receive-only double breast coil which had a side access (MRI Devices, Milwaukee, North America) (Figure 10.1). The breast was stabilised by compression plates within the coil, and the needles were carefully positioned so that they projected into the side access of the breast coil.

![Breast coil with a limited side access](image)

*Figure 10.1:* Breast coil with a limited side access

In the present study an attempt was made to obtain pre-treatment contrast-enhanced MR images in all patients with the aim of staging and defining the enhancement characteristics of the cancer. However, this was possible in 10 patients only mainly due to time constraints - patient and scanner time. In 6 of the 10 patients the pre-treatment MR images were obtained immediately before starting laser therapy and consequently the tumour was enhanced at the start of treatment.

Dynamic MR monitoring was performed using the double breast coil with a side access, in a single breast mode position. The needle position was confirmed on T1-weighted spin echo localiser images (TR/TE = 300/15 msec, FA90°, NEX 1, 192x256 matrix, 3 slices, 5-10 mm effective slice thickness, 350mm FOV, acquistion time 1.59 min). In view of the significant artefact seen due to the MR compatible needle, the needles were slid back over
the optical fibres out of the breast tissue in some cases. The optical fibres were pre-marked with an indelible marker at several measured points to ensure that the fibre tip was still in the correct position after needle removal.

To monitor the progress of therapy, a two-dimensional FLASH sequence was used (TR/TE = 111/10 msec, FA 60°, NEX 1, 3 slices, 10 mm-slice thickness, 3 sections, no gap, 128 x 256 matrix, FOV 350mm) and the images acquired every 30 s during and for 1 minute after laser treatment.

The dynamic images acquired during therapy were analysed on the operating console at the end of treatment. A gradually expanding zone of reduced signal intensity around the tip of each laser fibre was observed during the period of laser activation. The edges of the zone of signal loss were fairly well defined in all cases and allowed accurate measurements. The maximum transverse and vertical diameters of the area of signal loss were measured on the operating console on all the images acquired every 30 s. The extent of signal loss was subsequently correlated with the histological extent of laser induced necrosis.

Immediately after treatment, an attempt was made to obtain contrast-enhanced MR scans with the aim of identifying changes in the enhancement characteristics of the tumour as observed in chapters 8 and 9. However, this was possible in six patients, 2 of whom were also able to have further delayed contrast-enhanced MR scans at 48 h and 96 h after ILP respectively.

In all cases, surgery was undertaken as planned at the time of diagnosis on the basis of the clinical and mammographic findings of the extent of disease. The surgery was performed at a median interval of 2 days (range, 1 - 12 days) after laser therapy. Nine patients underwent wide local excision, and 5 underwent mastectomy. All but one patient underwent full axillary node clearance.

The specimens were delivered fresh to the laboratory immediately after surgery. All specimens were evaluated with serial sectioned pathological analysis and compared with the transverse MR images.

**Statistical analysis**

Linear regression analysis was used to compare final extent of signal loss on dynamic MR and histopathological measurements of laser induced necrosis.
10.3 RESULTS

In the 10 patients who had pre-treatment contrast-enhanced MR scans, the images showed a unifocal enhancing mass in all but one patient. In the latter patient, a curvilinear zone of diffuse enhancement was seen extending over two breast quadrants. The median maximum diameter of the tumour on the pre-treatment images (MR and/or US) was 20mm (range, 10 - 42mm). A single fibre was used for ILP in the first six patients studied irrespective of tumour size and in the remaining eight patients, the number of fibres used were increased with the aim of increasing the extent of tumour necrosis.

10.3.1 Single fibre treatments

Table 10.1 summarises the results in the six patients treated with a single fibre treatment. The onset of signal loss was seen at 30 s into treatment in three patients and at 60 s in the remaining three patients. In three patients, an additional zone of signal loss extending from the main zone of signal loss was seen radiating intermittently into the breast parenchyma. Figure 10.2 shows the changes in the extent of signal loss seen around the fibre tip during the period of laser activation and for one minute after laser deactivation. The median diameter of signal loss at the end of treatment was 14mm (range, 11-21mm).

Review of the dynamic MR images suggested a significant therapeutic effect within the tumour area in only one patient. In the remaining five patients the laser effect was thought to be at the tumour margin in three patients (Figure 10.3), and within the fat of the breast in the remaining two. These findings were confirmed on visual comparison of the dynamic images with the baseline images in four patients. In one of the 4 patients, in whom ILP was undertaken immediately after performing the 3D contrast-enhanced FLASH images, the dynamic images clearly showed the therapeutic effect occurring at the tumour margin, and extending into the fat of the breast (Figure 10.3).

Immediate post ILP contrast-enhanced MR images were obtained in four patients but these underestimated the laser effect compared with that identified on per-procedural monitoring. A therapeutic effect within the enhancing tumour was seen in one patient only (Figure 10.4). MR images in the remaining three patients showed an enhancing mass with the MR needle tip proximal to the tumour in one patient, the MR needle inserted into but through the enhancing mass in one patient, and signal loss in the fat posterior to the enhancing tumour in the other.
### Table 10.1: Summary of results in patients treated using a single fibre

<table>
<thead>
<tr>
<th>Patient/age</th>
<th>Pre-treatment lesion size (mm)</th>
<th>Dynamic MR signal loss at end of ILP (mm)</th>
<th>contrast-enhanced post-treatment MR: enhancing zone (mm)</th>
<th>contrast-enhanced post-treatment MR: nonenhancing zone (mm)</th>
<th>interval: ILP-surgery (days)</th>
<th>Histology: residual tumour</th>
<th>Histological laser-induced necrosis (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AB 64</td>
<td>15</td>
<td>13</td>
<td>15</td>
<td>0 h - no effect seen 96 h - 10 (fat)</td>
<td>12</td>
<td>11mm, G1, IDC</td>
<td>5 (fat)</td>
</tr>
<tr>
<td>DB 71 (Fig 10.3)</td>
<td>20*</td>
<td>21 a</td>
<td>not done</td>
<td>not done</td>
<td>1</td>
<td>20mm, G2, IDC</td>
<td>7 (tumour necrosis) + 18 (fat necrosis)</td>
</tr>
<tr>
<td>AG 38</td>
<td>15 (US)</td>
<td>12 a</td>
<td>14 b</td>
<td>0</td>
<td>2</td>
<td>15mm, G3, IDC</td>
<td>5 (fat)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>foci of cribriform-DCIS present up to 7 mm from tumour</td>
<td></td>
</tr>
<tr>
<td>DP 72</td>
<td>20</td>
<td>12</td>
<td>not done</td>
<td>not done</td>
<td>2</td>
<td>23mm G2, IDC</td>
<td>8 (eccentric tumour necrosis)</td>
</tr>
<tr>
<td>JP 41 (Fig 10.4)</td>
<td>42 (US)</td>
<td>14</td>
<td>26</td>
<td>12</td>
<td>0</td>
<td>22mm G2, IDC</td>
<td>17 (central tumour necrosis)</td>
</tr>
<tr>
<td>SH 48</td>
<td>28</td>
<td>16 a</td>
<td>25 c</td>
<td>0</td>
<td>4</td>
<td>26mm G2, IDC</td>
<td>5 (tumour necrosis) + 5 (fat necrosis)</td>
</tr>
</tbody>
</table>

* contrast-enhanced MR scan obtained immediately before treatment

a additional zone of signal loss extending from the main zone of signal loss seen radiating intermittently into breast parenchyma

b needle tip 1cm proximal to tumour
c signal loss seen in the region of the needle which is inserted into but through the mass
Figure 10.2: Graph showing changes in the extent of signal loss on "real-time" MR imaging during single fibre ILP treatment.
Figure 10.3: Contrast-enhanced MR images with MR compatible needle in position within a 20mm tumour. At the start of ILP, the needle was moved out of the breast with an attempt to leave just the optical fibre in position within the tumour. Real time 2D FLASH MR images obtained at (B) 60 s (C) 120 s (D) 300 s into treatment show an evolving zone of signal loss at the margin of the tumour and mainly within the fat of the breast (straight arrow). The tumour continues to have well defined margins until 60 s into treatment, but thereafter becomes ill defined due to contrast washout (C-D). Macroscopic examination (E) shows the laser "burn" mainly within the fat of the breast (long arrow) and involving just the margin of the tumour (short arrows).
Figure 10.4: Transverse (a) unenhanced and (b) gadolinium-enhanced T1W MR images obtained immediately after ILP using a single fibre show a 12mm nonenhancing zone at the needle tip (arrowheads) within the residual enhancing tumour (short arrow). Note the artefact due to the MR compatible needle in position within the breast (long arrow). This is the only patient in whom immediate post ILP MR images correlated closely with histological findings.
10.3.2 Multiple fibre treatments

Table 10.2 summarises the results of multiple fibre treatments. Of the eight tumours treated with more than one fibre (5 tumours x 2 fibres; 1 tumour x 3 fibres; 2 tumours x 4 fibres), a single coalesced zone of expanding signal loss was seen in five treatments. In the remaining three treatments, an additional separate zone of expanding signal loss was seen which was within the pectoralis muscle in two cases, and in the breast parenchyma in one case. In three patients, a “pull-back” technique was used for ILP treatment. In each of these cases following one cycle of treatment, the fibres were withdrawn by 5 - 10 mm and the laser fired a second time. In the interval prior to the start of the second part of the ILP treatment (approximately 10 minutes), the extent of signal loss seen at the end of the first treatment decreased significantly but had not completely resolved. Similar to the observation seen during single fibre ILP treatment, an additional zone of signal loss extending from the main zone of signal loss was seen radiating intermittently into the breast parenchyma. In both cases, the former zone of signal loss had smooth margins with a wave-like appearance, probably representing heat dissipation into a nearby blood vessel.

Figure 10.5 shows the changes in the extent of signal loss during ILP in the tumours treated with multiple fibre therapy. The onset of signal loss was seen at 30 s in all but one case, and reached its peak at a median interval of 270 s (range, 210 - 420 s) into treatment. The zone of signal loss was not completely homogeneous, but had regions of complex signal intensities within it in some cases (Figure 10.6). The median diameter of signal loss at the end of treatment was 27 mm (range, 12 - 47 mm) (excluding the additional zone of signal loss seen in the pectoralis muscle in two patients). In all cases there was a slight drop in the extent of signal loss in the first minute after laser deactivation.

Review of the dynamic images was suggestive of complete tumour ablation in three patients, greater than 50% tumour ablation in two, and minimal therapeutic effect within the tumour in the remaining three. These findings were further confirmed on visual comparison of the dynamic images with the baseline images in six patients. In five of the latter six patients, ILP was undertaken immediately after performing the contrast-enhanced 3D FLASH images. In two patients, the enlarging zone of signal loss completely replaced the enhancing tumour including a margin of surrounding fat during ILP (Figure 10.7), and in the remaining three patients, the zone of signal loss overlapped only part of the enhancing tumour during therapy but extended into the adjacent breast tissue (Figure 10.8).

Immediate post-treatment contrast-enhanced MR images were obtained in two patients (who had not had contrast-enhanced images just before ILP) which showed a much smaller effect than that identified on per-procedural monitoring. In one patient, the
immediate post-treatment MR images showed two non-enhancing zones measuring 8mm and 12mm in diameter respectively within an enhancing mass (Figure 10.6). However, similar images performed at 48 h post therapy in the same patient showed a diffuse area of increased signal intensity with no evidence of contrast-enhancement. To further understand these findings, subtraction imaging was performed which showed a central non-enhancing zone with a peripheral rim (1mm) enhancement (Figure 10.6). MR images in the remaining one patient showed an irregular enhancing mass with signal loss predominantly in the fat of the breast.
Table 10.2: Summary of results in patients treated using multiple fibres

<table>
<thead>
<tr>
<th>Patient/age</th>
<th>Pre-treatment lesion size (mm)</th>
<th>number of fibres</th>
<th>Dynamic MR signal loss at end of ILP (mm)</th>
<th>contrast-enhanced post-treatment MR: (a) enhancing zone (b) nonenhancing zone (mm)</th>
<th>interval ILP - surgery (days)</th>
<th>Histology: residual tumour (mm)</th>
<th>Histological laser-induced necrosis: necrosis (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>JF 68</td>
<td>16 (US)</td>
<td>2</td>
<td>29 a</td>
<td>(a) 14 (b) 12 (fat)</td>
<td>1</td>
<td>12mm, G2, IDC</td>
<td>8 (tumour necrosis) + 16 (fat necrosis)</td>
</tr>
<tr>
<td>JW 86</td>
<td>36</td>
<td>2</td>
<td>23 a</td>
<td>not done</td>
<td>5</td>
<td>30mm mucoid carcinoma</td>
<td>12 (eccentric tumour necrosis)</td>
</tr>
<tr>
<td>CB 68</td>
<td>32 *</td>
<td>2</td>
<td>16 (fat) (CB-F) 12 (tumour area) (CB-T)</td>
<td>not done</td>
<td>2</td>
<td>comedo-type microinvasive DCIS</td>
<td>13 (fat) + 10 (central tumour necrosis)</td>
</tr>
<tr>
<td>VH 79</td>
<td>20 *</td>
<td>2</td>
<td>32</td>
<td>not done</td>
<td>3</td>
<td>10mm, G2, IDC, (viable tumour in superior margin)</td>
<td>31 (extends into muscle)</td>
</tr>
<tr>
<td>MC 51 (Fig 10.8)</td>
<td>27 *</td>
<td>2 + P</td>
<td>38 a</td>
<td>not done</td>
<td>5</td>
<td>12mm, G2, IDC, (viable tumour superior margin)</td>
<td>34 (extends to fat),</td>
</tr>
<tr>
<td>LJ 58</td>
<td>10 *</td>
<td>3</td>
<td>21 (tumour area) 19 (pectoralis muscle) (LJ-M)</td>
<td>not done</td>
<td>5</td>
<td>0</td>
<td>28 (9mm &quot;in-situ&quot; tumour fixation)</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td>AW</td>
<td>28 (US)</td>
<td>4 + P</td>
<td>26</td>
<td>immediate post ILP (a) 34 (b) 8, 12 48 h post ILP * (a) 1 (b) 32</td>
<td>8</td>
<td>0</td>
<td>31 (12mm &quot;in-situ&quot; tumor fixation)</td>
</tr>
<tr>
<td>HW</td>
<td>21 *</td>
<td>4 + P</td>
<td>47 (tumour area) 14 (pectoralis muscle) (HW-M)</td>
<td>not done</td>
<td>10</td>
<td>0</td>
<td>45 (14mm &quot; in-situ&quot; tumor fixation)</td>
</tr>
</tbody>
</table>

a additional zone of signal loss extending from the main zone of signal loss seen radiating intermittently into breast parenchyma

* contrast-enhanced MR scan obtained immediately before treatment

P - Pull-back treatment (2nd ILP treatment)
Figure 10.5: Graph showing changes in the extent of signal loss on "real-time" MR imaging during multiple fibre ILP treatment.
Figure 10.6  MR images of a multiple fibre ILP treatment with the MR compatible needles in position throughout the treatment (long arrow in A). Images obtained at (A) 60s (B) 120 s (C) 210 s (D) 500 s into treatment showing the evolving zone of signal loss (short curved arrow in A-D).
Figure 10.6: Similar images (E-H) obtained during the 2nd ILP treatment with the fibres pulled back within the tumour.
Figure 10.6: Contrast-enhanced MR images obtained immediately after ILP (I) show an 34mm enhancing mass with two nonenhancing zones measuring 8 and 12mm in diameter (arrowed). Similar images obtained 48 h after ILP (J) before and (K) after ILP show an area of increased signal intensity without contrast enhancement. Subtraction imaging (L) shows a 32mm central nonenhancing zone with a peripheral thin (1mm) enhancing rim.
Figure 10.6: Microscopic examination (M) shows complete tumour ablation seen as a 12mm zone of "in-situ" tumour fixation (curved arrows) within a 31mm diameter zone of necrosis (short arrows at the margins of the zone of laser-induced necrosis). High power view (N) shows the zone of "in-situ" tumour fixation as a mucinous matrix (H&E stain, original magnification x1.5).
Figure 10.7: MR images obtained immediately prior to starting ILP show, before (a) and after (b) contrast-enhancement a 21mm enhancing mass in the upper outer quadrant of the left breast. Dynamic 2D FLASH MR images obtained at the end of ILP (c) show an area of signal loss measuring 42x18mm within the breast parenchyma that has completely occupied the site of the enhancing tumour and, a further area of signal loss measuring 14mm within the pectoralis muscle. The signal loss in the muscle correlated with muscle necrosis seen at surgery.
Figure 10.7: Microscopic examination shows (d) complete tumour ablation seen as a 14mm zone of "in-situ" tumour fixation (curved arrow) within a 45mm zone of laser induced necrosis (H&E stain, original magnification x1.5). The charred zones of cavitation corresponding to the fibre tip position are marked (short arrows). High power views (x10) show (e) the zone of "in-situ" tumour fixation characterised by smeared hyperchromatic nuclei and a preserved morphological appearance.
Figure 10.8 Contrast-enhanced 2D FLASH coronal MR images obtained during multiple fibre treatment of a 27mm tumour show (A) an enhancing tumour (straight arrow) with signal loss in its inferior aspect (curved arrow). Real time MR images obtained at (B) 210 s and (C) 410 s show an increase in the area of signal loss that has replaced part of the enhancing tumour. The residual enhancing tumour is marked with an open arrow. The short arrow indicates the MR compatible needles within the breast. Microscopic examination (D) shows residual tumour at the superior margin only (short arrow) (H&E stain, original magnification x 1.5).
10.4.3 Histopathological correlation

The median diameter of laser necrosis within the breast parenchyma in the six single fibre treatments was 9 mm (range, 5 - 20mm) and in the eight multiple fibre treatment was 28mm (range, 10 - 45mm). These correlated closely with the site and extent of signal loss at the end of laser treatment on dynamic imaging ($r^2=0.85$) (Figure 10.9). In one patient, additional foci of DCIS were present beyond the margins of the index tumour but were not depicted on the pre-treatment contrast-enhanced MR images.

Figure 10.9 Scatter diagram showing correlation between the extent of signal loss at the end of ILP treatment on dynamic MR imaging and histological extent of laser induced necrosis.

On the immediate post ILP contrast-enhanced MR images obtained in 7 patients, the non-enhancing zone underestimated significantly the extent of histological necrosis in all but one patient. In the latter patient treated using a single fibre, the nonenhancing zone measured 12mm, and the histological necrosis measured 17mm (Figure 10.4). On the MR images obtained at 48 and 96 h after ILP in two patients, the non-enhancing zone correlated closely with the histological extent of laser induced necrosis (Figure 10.6 J - N).
10.3.4 Complications

Two types of complication were seen. A pectoralis muscle burn was seen in 3 cases, all treated with multiple fibres. In two cases, dynamic images showed a separate zone of signal loss within the pectoralis at 30 s into treatment. The diameter of signal loss at the end of treatment in these two cases was 14mm (Figure 10.7) and 19mm. In the third case, a single coalesced zone of signal loss within the tumour area was seen which extended to the underlying muscle during therapy. In all three cases, the tumour was close to the underlying muscle and it is likely that one of the fibres had slipped into the muscle during fibre/needle positioning. In all three cases, muscle necrosis was confirmed during surgery but this was very localised and caused the patient no problems in the interval to surgery. The second complication was a skin bum, seen in 1 patient treated with 4 fibres and a "pull-back" technique, where it is likely that the tip of one fibre may have moved too close to the skin while the patient was within the scanner. The area of skin bum measured 1cm and was excised as part of the subsequent surgery.

10.4 DISCUSSION

The results of the present study are in broad agreement with previous reports on the usefulness of T1-weighted 2D FLASH sequence for the per-procedural monitoring of interstitial laser therapy of malignant tumours (Kahn et al, 1994; Vogl et al, 1995, Roberts et al, 1997b). In addition, our study also provides histological correlation with the final area of signal loss seen on dynamic imaging which has been lacking in previous clinical studies. These results are in agreement with those reported recently by Roberts et al (1997a). In the latter study, the authors correlated signal loss seen on T1-weighted spin echo and FLASH sequences during ILP of normal rat liver with histological extent of tissue necrosis assessed by diaphorase staining. The signal intensity changes on FLASH images were more complex than those observed with spin echo images but interestingly allowed a better correlation with histological extent of tissue necrosis ($r^2 = 0.95$ versus $r^2 = 0.88$).

In the present study, we have shown how the area of signal loss changes on dynamic MR imaging during the period of laser activation. Our results demonstrate the onset of signal loss as early as 30 - 60 s from the start of treatment. In contrast, the hyperechoic changes seen during real-time ultrasonography of ILP in breast tumours usually appear after a delay of approximately 100 s from the start of treatment (Mumtaz et al, 1996). This may be related to the decreased sensitivity of ultrasound compared with MR imaging in demonstrating laser effects (Castro et al, 1990). In the present study, the peak signal loss on dynamic MR was seen 270 - 420 seconds into treatment similar to the time of onset of
the maximum hyperechoic change seen during dynamic ultrasonographic monitoring of ILP (Mumtaz et al, 1996). The maximum hyperechoic zone seen on real-time ultrasonography tends to remain approximately the same size and shape until the end of laser therapy, and has been shown in previous studies to correlate poorly with the histological extent of laser induced necrosis. In contrast, the results of the present study show that the extent of signal loss at the end of laser therapy correlates accurately with the histological extent of laser induced necrosis.

We have not attempted to quantify the changes in signal intensity seen on dynamic imaging or correlate these to temperature measurements. A recent study on dynamic MR imaging of ILP in ex vivo rabbit liver showed the signal intensity changes at the margins of the evolving hypointense zone seen during therapy did not show an inverse relationship with temperature change but the bright signal characteristics (hyperintense margin) of a secondary thermal effect at the lesion edge seen immediately post ILP accurately demarcated the ILP zone of necrosis. (Fried et al, 1996). The latter study was designed to fill the drawbacks of previously reported ILP/temperature experiments that have shown a 0.5 - 1.1% decrease in signal intensity per degree Celsius in ex vivo liver (Matsumoto et al, 1992a, 1994). The temperature sensitivity of various MR parameters can only be exploited for detecting temperature changes within a critical range (Jolesz et al, 1988). Lewa and Majewska (1980) reported an irreversible decrease in T1 at temperatures greater than 40°C due to alteration of macromolecule-water interactions which occurs before the obvious denaturation of proteins at 60°C. The fluctuations in the zone of signal loss during therapy and the slight reduction in the extent of signal loss seen during the first minute after ILP in the present study may represent the reversible components of the signal loss.

The results of our study suggest that the edge of the area of signal loss seen during treatment on dynamic imaging can be used reliably to monitor and potentially control the progression of laser induced necrosis. This might be refined further by developing a feedback-control system so that once the desired volume of signal loss is achieved, or if the signal loss gets unacceptably close to vital structures, the laser is automatically switched off. In the present study, the assessment of the extent of tumour necrosis and residual tumour was made by visual comparison of the pretreatment contrast-enhanced MR images with the dynamic images. However, this approach could be refined if the area of signal loss could be segmented, or colour coded and superimposed on the baseline images so untreated areas of the tumour could be recognised and treated if necessary, with repositioning of the fibres.

In six patients, ILP was performed immediately after acquiring 3D contrast-enhanced MR images. The advantages of such an approach included accurate definition of tumour margins at the start of treatment which is difficult on the unenhanced T1-weighted
images. Secondly, it allowed improved visualisation of the evolving zone of signal loss by improving contrast between the tissue with the contrast-material (high signal) and the treatment effect (low signal). The pharmacokinetics of intravenous Gd-DTPA in malignant breast tumours is variable but shows a rapid uptake followed by rapid washout into the normal breast tissue. Thus, although with the progress of laser therapy the tumour margins become less clearly defined due to contrast washout, the presence of contrast-material within the remaining breast tissue improves visualisation of the evolving zone of signal loss. Thirdly, by obtaining the pre-treatment images at the same time as the dynamic images, a near accurate comparison between the two can be made as the breast remains in the same position within the breast coil. The safety of MR imaging contrast media when exposed to high temperatures observed during ILP has been investigated in \textit{in vitro} studies and have demonstrated complete stability of the gadolinium chelate (Meibner et al, 1995). Dynamic MR imaging of ILP immediately post contrast-material injection has not been reported previously to our knowledge but it appears promising, and needs to be further evaluated.

Changes seen on immediate post-therapy contrast-enhanced MR imaging did not accurately reflect the effects seen during therapy or with the histological extent of tissue necrosis confirming our earlier experience (Mumtaz et al, 1996). However this is not in keeping with the experience of others (Kahn et al, 1994; Vogl et al, 1995). Kahn et al (1994) observed that the lesion size on 2D FLASH scans during therapy of malignant brain tumours correlated well with the total lesion size on 3D turboFLASH scans post Gd-DTPA after therapy. The latter MR images showed a central non-enhancing zone with a peripheral enhancing rim which was included in the measurement of total lesion size. Vogl et al (1995) showed that contrast-enhanced dynamic T1-weighted turboFLASH and 2D-FLASH imaging performed immediately after treatment provided important information on perfusion changes in the central and peripheral part of treated colorectal liver metastases but did not correlate these with the extent of signal loss seen during laser therapy or with delayed contrast-enhanced computed tomography. In addition, both studies lacked histological confirmation of their observations.

In the present series, we were only able to target the ILP reasonably accurately in 50% of cases. The problems related mainly to the restricted access for fibre / needle manipulation through the narrow side access of the breast coil used in the present study. In addition, breast immobilisation and fibre immobilisation were inadequate. Consequently the fibre slipped in too far in the cases where only the tumour margin was treated or the tumour was missed. In some cases where we attempted to slide the MR compatible needle back over the optical fibre out of the breast, the fibre may have moved out of its correct position during the manoeuvre. Artefacts associated with MR compatible needles can obscure small lesions and make the signal intensity changes occurring during treatment difficult to evaluate accurately. MR compatible needles which cause less susceptibility
artefact than those commercially available are necessary when working at this field strength (1 Tesla). Marking the optical fibre with magnetite markers as reported by Vogl et al (1995) may aid accurate positioning of the fibre within the tumour area. Several recent studies have evaluated and refined the techniques of MR guided breast biopsies, particularly for clinically and mammographically occult additional enhancing foci (Orel et al, 1994b; Doler et al, 1996). Using similar technology, it may be possible to position optical fibres at the time of obtaining tissue for histological examination.

One of the main limitations of dynamic MR imaging presently, is the lack of true ‘real time’ imaging. With the technology available to us in this study, the therapeutic effects could be reviewed only at the end of treatment. Thus the complications we encountered in this study were not recognised until at the end of treatment. Analysis of our time-signal loss curves suggest that image reconstruction and display as early as 60 - 90 seconds would help guide treatment.

There are a number of techniques under development which will improve MR monitoring of laser therapy by improving spatial and temporal resolution. An open configuration MR system has recently been tested, and the results appear promising (Schenck et al, 1995). The system allows accurate targeting of lesions that need tissue diagnosis, image feedback is near "real-time" and the procedure is interactive (Silverman et al, 1995).

10.5 CONCLUSION

The results of the present study confirm that per-procedural MR appearances correlate accurately with the extent of tissue destruction by ILP. This opens the way for MR monitoring of laser therapy in breast cancer with the new generation of interventional MR scanners.
CHAPTER 11: IMAGE GUIDED ILP IN THE TREATMENT OF FIBROADENOMAS

11.1 INTRODUCTION

11.2 PATIENTS AND METHODS

11.3 RESULTS
   11.3.1 Clinical observation
   11.3.2 Ultrasonography
   11.3.3 Breast MR imaging
   11.3.4 Complications

11.4 DISCUSSION

11.5 CONCLUSION
11.1 INTRODUCTION

The results in chapter 8-10 have illustrated the potential role of ILP in the treatment of breast cancer. Its role in the treatment of benign breast tumours has not been previously reported. The clinical requirements for the application of ILP in the treatment of fibroadenomas need not be as strict as those for the treatment of breast cancer. Although the aim of therapy is to ablate the entire volume of the tumour, there is no risk to the patient if part of the lesion is left untreated.

The clinical question that needs to be addressed is why treat fibroadenomas with ILP and what are the proposed benefits of the latter form of therapy over conventional treatment.

As the majority of fibroadenomas can be accurately diagnosed using a combination of clinical examination, ultrasonography and fine needle aspiration cytology (Smallwood et al., 1988) the philosophy of its routine excision has been questioned and recent studies have confirmed the safety of conservative management of such breast lumps (Carty et al., 1995; Dixon et al., 1996). However, the patient acceptability of conservative management has varied widely in different studies with 21% to 90% opting for such treatment (Cant et al., 1987; Dixon et al., 1996). This is in part due to the uncertain natural history of untreated fibroadenomas. The percentage of breast lumps indicated by clinical and cytological assessment to be fibroadenomas resolving spontaneously over a period of 1-3 years has been reported as no more than 16-37% (Sainsbury et al., 1988; Dent et al., 1989; Wilkinson et al., 1989). On the other hand, surgical excision carries the risks of anaesthesia, haemorrhage, infection, and scarring, which particularly with recurrent or multiple fibroadenomas, may be disfiguring. In addition, surgical excision of all benign breast lumps would result in a very large workload.

In light of the above pitfalls in the conventional management of fibroadenomas, the technique of ILP was investigated to provide a minimally invasive approach for the localised ablation of fibroadenomas. The laser and optical fibre parameters and imaging techniques used in the present study are based on the work described in chapters 8-10.

11.2 PATIENTS AND METHODS

In our institution, all patients under the age of 35 years presenting with a discrete palpable breast lump(s) that is proven on clinical, ultrasonographic and cytological examination (benign sheets of epithelium in a background of bare nuclei) to be a fibroadenoma are offered the choice of conservative management with regular follow up or surgical excision if requested. In the present study, the patients (n = 15) were selected from the group that was initially keen on surgical excision, and treated with ILP in the interval prior to surgery. The median age of this group was 25 years (range, 19 - 34 years). All
patients gave written informed consent for participation in this study which was approved by the ethics committees for human research at University College Hospital, London, and Royal Surrey County Hospital, Guildford.

Immediately prior to ILP, patients were given intravenous diazepam (5-10mg) and pethidine (50-100mg). After localisation and measurement of the tumour by ultrasound (Aloka 650 [7.5Mhz breast probe]; Aloka, Tokyo, Japan), 5 - 10mls of 1% lignocaine was infiltrated into the skin and the peritumoural breast tissue. One - four 19 gauge needles were inserted percutaneously into the tumour under ultrasound guidance, with the needle tips positioned about 1cm apart within the tumour. The technique of ILP used is detailed in chapters 8 and 9. The number of fibers used were roughly matched to the size of the lesion, with the aim of just treating the lesion itself and avoiding the adjacent normal breast tissue.

All treatments were monitored with real time ultrasonography, and the maximum extent of thermal change (seen as an expanding zone of increased echogenicity) was measured. Serial ultrasonographic examinations were performed at 2 weeks post treatment and at 1 - 2 month intervals thereafter. In all cases, the maximum diameter of the lump was measured.

Pre-treatment MR imaging of the breast was performed in seven patients only. The technique used was similar to that described in chapter 3. The post-treatment MR images were performed at an interval of 2 - 6 weeks after ILP.

11.3 RESULTS

All patients in the present study had a palpable lump for a duration of 12 - 24 months (median, 12 months) before presentation. In all cases, the lump had either remained static or increased in size in the few months prior to presentation. The median ultrasonographic size of the lump at presentation was 26mm (range, 14 - 35mm).

Laser therapy was undertaken using 1 - 4 fibers, such that the extent of laser induced necrosis roughly matched the size of the lump being treated (lumps < 15mm: 1 fibre, 15 - 25mm : 2 fibres, > 25mm : 4 fibres). Real time (per procedural) ultrasound monitoring was undertaken in all patients. The ultrasonographic changes seen during ILP were similar to those observed in the treatment of malignant breast tumours as described in chapter 8 (Figure 11.1). Immediately post treatment the lump appeared diffusely echogenic on ultrasonographic examination, with no clear demarcation between the area of laser induced necrosis and residual tumour.
11.3.1 Clinical observation

All patients tolerated the laser procedure satisfactorily with the use of intravenous analgesia and sedation. Immediately post treatment the lump appeared to increase in size on palpation and on patient self examination although the increase in ultrasonographic measurement was no more than a few millimeters in all cases. Overlying skin bruising was seen in 4 cases with relatively superficial lesions. The peritumoural oedema and skin bruising resolved within one week in all cases. Post-treatment analgesia and antibiotics were not required in any patient. All patients returned to their routine work the day after ILP, although they felt the treated breast to be sensitive to touch for a period of 1 - 5 weeks (median, 1 week). The size and shape of the breast was preserved in all cases.

11.3.2 Ultrasonography

At follow up, there was a reduction in the size of the treated fibroadenoma in all patients. Ten of the 15 patients rejected surgical excision and elected to be followed up conservatively. In this group, the response to therapy was evaluable by serial ultrasonography in 9 patients. On serial ultrasonography, the increased echogenicity seen at the end of ILP persisted in some but not all tumours. Other changes seen on ultrasonography during follow up included cavitation in two tumours, and irregular margins of the treated lump in all cases (Figure 11.1). In one patient, ultrasonographic measurement post-treatment was particularly difficult, possibly due to the destruction of the capsule during laser therapy. In this patient, the change in the size of the lump was monitored by clinical examination. At 8 weeks post treatment, the mean reduction in tumour size in the 10 patients managed conservatively was 45% (range, 28% - 60%). At a median follow up of 5 months (range, 3 - 6 months), the mean reduction in tumour diameter was 75% (range, 48% - 100%) (Figure 11.2). In 3 patients, the lump had completely resolved on clinical, ultrasonography and patient’s self examination.
Figure 11.1 Ultrasonographic images of right breast fibroadenoma in a 26-years old female shows (a) before treatment a 28 mm well defined mass (b) during laser treatment shows an expanding echogenic zone (c) at 4 weeks post-treatment a mass with ill defined borders measuring 22 mm in transverse diameter and (d) at 6 months follow up a residual 9 mm mass.
Figure 11.2: Graph showing changes in the size of the fibroadenoma after interstitial laser photocoagulation (triangle symbols represent ultrasonographic measurements, black circle represents the patient in whom clinical measurement was used at follow up)
Five patients underwent surgical excision of the treated fibroadenoma. This was performed at a median interval of 4 weeks (range, 2 weeks - 6 months) after ILP. Table 11.1 summarises the results in this group of patients. In all cases, ultrasonographic measurements of the treated lump immediately prior to excision correlated closely with the histological size of the resected lump. The mean reduction in tumour size on ultrasound at the time of excisional biopsy compared with that at presentation was 21% (range, 18% - 50%). In one patient, although there was a 50% reduction in tumour size at 6 months after ILP, a lump was still clinically palpable and the patient requested surgical excision. Histological examination of the tumour showed predominantly areas of elastosis and fibrous tissue measuring 10mm in maximum dimension, with an eccentric 6mm area of residual fibroadenoma. In the tumours excised at 2 weeks post-ILP, the histological features (macroscopic and microscopic) were similar to those seen in the treatment of malignant tumours (Figure 11.3).

**Table 11.1:** Results in patients that underwent surgical excision of the laser treated fibroadenoma.

<table>
<thead>
<tr>
<th>Patient age</th>
<th>Pretreatment US</th>
<th>Hyperechoic zone after treatment</th>
<th>Time from ILP to surgery (weeks)</th>
<th>US size immediately prior to surgery</th>
<th>Histological size of lump</th>
<th>residual tumour within lump</th>
</tr>
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<tr>
<td>22</td>
<td>22</td>
<td>8</td>
<td>2</td>
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<td>28</td>
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<td>3</td>
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<tr>
<td>29 *</td>
<td>34</td>
<td>12</td>
<td>4</td>
<td>27</td>
<td>30</td>
<td>2</td>
</tr>
</tbody>
</table>

All measurements represent maximum diameter (mm) of relevant zones

* post therapy MR imaging at 2 weeks showed a 28mm central non-enhancing zone with a 2mm peripheral enhancing rim

**11.3.3 Breast MR imaging**

Seven patients had MR imaging before and after ILP treatment. In four patients, the pre-treatment MR images showed a discrete, strongly enhancing mass with well defined borders. Following ILP, a new well defined central zone of non-enhancement developed within the tumour, surrounded by a thin peripheral enhancing zone. In 3 patients, all of whom declined surgery, comparison with pre-treatment MR images suggested near complete ablation of the fibroadenoma (Figure 11.4). One of these 4 patients elected for surgical excision (Table 11.1), and in this patient the central non-enhancing zone
corresponded with necrotic tissue and the peripheral enhancing rim with residual tumour (Figure 11.5).

In the other 3 patients imaged with MR, the pre-treatment scan showed architectural distortion at the site of the clinically palpable lump but without contrast enhancement. Post therapy contrast-enhanced MR imaging did not show any new changes.

*Figure 11.3:* (a) Macroscopic appearance of laser treated fibroadenoma excised at 2 weeks post-ILP. The tumour is cut through its centre and shows a central zone of cavitation and an outer haemorrhagic rim. Note the additional volume of breast tissue excised along with the fibroadenoma. Microscopic examination shows a clear separation between the zone of coagulative necrosis and residual tumour (short arrows), which correlated with the haemorrhagic rim seen on macroscopic examination.
Figure 11.4: Pretherapy transverse T1-weighted MR images of right breast in a 29-years old female (a) before and (b) after contrast enhancement show a homogeneous enhancing mass measuring 28 mm in diameter and with well defined borders. MR images obtained two-weeks after interstitial laser photocoagulation show (c) before and (d) after contrast enhancement a non-enhancing zone that has almost completely replaced the previously enhancing mass.
Figure 11.5  (A) Macroscopic appearance of fibroadenoma excised at 4 weeks after ILP treatment. Transverse T1W MR images obtained at 2-weeks after ILP in the same patient show before (B) and after (C) contrast-enhancement a 28mm central nonenhancing zone with a peripheral 2mm enhancing rim (long arrow). The nonenhancing zone correlated accurately with histological extent of necrosis. The contralateral breast shows an enhancing mass proven on cytology to be a fibroadenoma (curved arrow).
11.3.4 Complications

The only complication of treatment seen in this series was a skin burn at the needle entry point in a patient treated with 4 fibres, in whom the lesion was located superficially in the breast. Immediately post-therapy, a 1 cm² area of skin showed erythema. One week after treatment, part of this had undergone full thickness necrosis with scab formation. This was subsequently managed by regular dry dressings and healed with minimal scar tissue over a period of 6 weeks. During this period the fibroadenoma decreased significantly in size, and at follow up at 16 weeks had resolved completely. Post-therapy MR images in this patient were suggestive of near complete tumour ablation. During the period of skin healing, there were no signs of wound infection and no prophylactic antibiotics were given.

11.4 DISCUSSION

Conservative management of breast fibroadenomas is a safe alternative to surgical excision in carefully selected patients in whom the lesion can be confidently diagnosed by combined clinical, cytological and ultrasonographic examination. However in view of the variable natural history and the fact that some lumps may continue to increase in size, outpatient follow up for a period of at least 2 years is essential before patients can be discharged. In the present study all fibroadenomas treated by ILP became smaller and two thirds of the patients declined surgical excision even though they had initially wanted surgery after ILP. In the group that underwent surgical excision, histological examination confirmed significant tumour necrosis.

The mean reduction in tumour size at 8 weeks post-therapy was 45%, and in all 10 cases opting for non-surgical management, there has been continuing reduction in tumour size with time. Dixon et al (1996) used the criteria of a 20% spontaneous reduction in tumour volume as being acceptable for continuing conservative management and discharged such patients from the clinic. Although the patient acceptability of this approach was high in the series reported by Dixon et al (1996), this was not the case in other studies (Dent et al, 1989; Wilkinson et al, 1989). Knowledge that over 50% of fibroadenomas remain static in size over a period of 2 years follow up and that some may increase in size is likely to reduce the acceptability of conservative management. In another series of fibroadenomas followed up for 5 years, only 32% resolved, with resolution being more frequent in those lesions that measured less than 12mm in diameter at presentation (Carty et al, 1995). In the present study, with a follow up of just 6 months, 3 fibroadenomas have resolved completely. Only one patient was dissatisfied with the result at 6 months and even in this case the tumour had shrunk to half the size it had been initially. With longer follow up, the percentage of laser treated fibroadenomas that resolve completely may increase. This
is only a pilot study, and as experience increases, it is likely that the number of fibres used and their positioning will be better matched to the volume and shape of each lesion so the percentage of completely ablated fibroadenomas should increase. Furthermore, there is no risk to patients if part of the lesion is left untreated, and as there is no cumulative toxicity, treatment can be repeated if necessary.

As the majority of fibroadenomas have a characteristic ultrasonographic appearance due to their well defined capsule, ultrasonography allows their size and volume to be monitored accurately in serial studies (Smallwood et al, 1988; Farouhi et al, 1994). In the present study, ultrasonographic measurements correlated closely with the histological measurements of excised specimens, and was useful in monitoring the size reduction of the treated lumps. However, accurate estimation of tumour size may be difficult in cases where the capsule is damaged by laser therapy. Ultrasonography also allows accurate needle and optical fibre positioning for ILP. Its limitations remain in defining the extent of laser induced necrosis and residual tumour (Harries et al, 1994; Mumtaz et al, 1996) such that further treatment if required cannot accurately be planned on the basis of ultrasonographic examination.

MR imaging has proved particularly valuable for monitoring ILP effects in breast cancer (Mumtaz et al, 1996) and so was also used in some of the cases in the present study. Pre-therapy MR imaging was used to look at the size and enhancement characteristics of fibroadenomas as it is known that not all fibroadenomas show contrast-enhancement. Contrast-enhancement correlates with their cellularity and water component (Gilles et al, 1995b). It is possible that lesions with poor cellularity are less likely to increase further in size, and may therefore not benefit from ILP, although as yet, there is no firm data on this. Post-therapy MR imaging proved valuable in defining the extent of necrosis and residual tumour only in tumours that enhanced before treatment. In the one patient that underwent surgical excision after MR imaging, the extent of necrosis and residual tumour was accurately mapped by post-treatment MR imaging.

There is little information on the morbidity associated with surgical excision of benign breast lumps. Dixon and coworker (1992), reported that up to 25% of patients having excision of benign lumps may have wound related complications. In retrospect, the single complication of a skin burn seen in this series was predictable. The lump in this patient was relatively superficial, and was treated with four fibres. It is likely that one of the fibres was too superficial. In undertaking interstitial laser therapy, care is needed to avoid damage to the skin and underlying muscle. For lesions close to skin or muscle, it may be safer not to try and ablate the entire lesion initially, but to repeat ILP later if necessary to remaining viable areas which can be identified on contrast-enhanced MR scans.
The main disadvantage of ILP compared with surgical excision of fibroadenomas is that it takes a long time for the area of laser induced coagulative necrosis to resolve. However, ILP has the major advantage of preserving the shape and size of the breast and avoiding the need for a surgical scar. Further, knowing that the laser treated lump is an area of coagulative necrosis rather than viable cells that may grow, is likely to make ILP an attractive alternative even to conventional conservative management, from the patients point of view.

11.5 CONCLUSION

In conclusion, interstitial laser photocoagulation has considerable potential as a technique for localised ablation of fibroadenomas. Adequate guidance and monitoring can probably be achieved with ultrasound, although MR imaging gives a more accurate picture of the extent of laser induced necrosis.
SECTION D: SUMMARY AND FURTHER RESEARCH

CHAPTER 12

12.1 MR IMAGING OF BREAST CANCER
   12.1.1 Implications for diagnosis and treatment
   12.1.2 Implications for prognosis
   12.1.3 Assessment of local recurrence in the conserved breast
   12.1.4 Assessment of response to neoadjuvant therapy

12.2 MR IMAGING OF ILP IN BREAST CANCER

12.3 FUTURE DIRECTIONS FOR ILP IN BREAST CANCER

12.4 FUTURE DIRECTIONS FOR ILP IN FIBROADENOMAS
The potential of MR imaging for evaluating breast disease is continuing to evolve with advances in MR imaging technology. Presently, however, the role of MR imaging in the routine management of patients with breast cancer is still in the investigational stage. The work presented in this thesis has addressed clinical situations in which MR imaging is likely to have a leading role in the management of patients with breast cancer. In this chapter, areas where further research is desirable is discussed.

12.1 MR IMAGING OF BREAST CANCER

12.1.1 Implications for diagnosis and treatment

Two basic technical approaches have been investigated in the literature for contrast-enhanced breast MR imaging: dynamic and static imaging. In the studies detailed in this thesis, static contrast-enhanced MR imaging showed a significant improvement in the locoregional staging of breast cancer compared with X-ray mammography. The incidence of false positive contrast-enhancement in the staging of primary breast cancer was 7%. Although analysis of time-intensity curves during dynamic imaging can improve the specificity of MR in distinguishing benign from malignant lesions, the high temporal resolution is usually obtained at the expense of spatial resolution, volume-of-view, signal-to-noise ratio, and or fat suppression, which can compromise sensitivity to small and multifocal cancers. Thus, a combination of rapid acquisition with techniques which preserve high spatial resolution would be ideal for breast MR imaging. These would improve specificity by allowing evaluation of lesion morphology as well as enhancement patterns. Presently, as contrast-enhanced MR imaging and MR guided biopsy procedures are both time consuming and expensive, an acceptable specificity value must be high.

Developments in image processing techniques such as fat suppression, and subtraction imaging including techniques allowing image reregistration to compensate for movement artefacts may further improve lesion detection and classification. Currently since both imaging techniques (dynamic and static techniques) yield numerous images, post-processing and evaluation methods need to be improved and standardised to ease interpretation.

The results in chapter 5 have shown the improved accuracy of contrast-enhanced MR imaging compared with X-ray mammography with regards to all parameters required for an accurate locoregional staging of primary breast cancer. In the present study, these results were not utilised in planning the first surgical treatment which was based purely on triple assessment. Of the 53 cancers treated by WLE, 17% had positive resection margins. Residual disease at reexcision was detected in 8 of these 17 patients, a finding that correlated closely with the extent of contrast-enhancement on MR imaging. Although
these results suggest that MR imaging would be useful in planning a single definitive resection, this observation needs to be confirmed in a prospective study in which treatment planning based on triple assessment versus assessment which includes MR imaging are compared. The results of such a study would provide important data on the extent to which the operative planning might change based solely on MR imaging. Further findings in this thesis on the accuracy of MR in the assessment of the nipple-retroareolar complex may enable planning a nipple preserving mastectomy is suitable patients.

Currently, all patients treated with breast-conservation surgery receive adjuvant radiation therapy to reduce the potential for recurrence from "subclinical" residual cancer. Consequently, even patients without multicentric disease are being treated with adjuvant radiation therapy as they cannot be accurately identified. Since radiation therapy accounts for a substantial portion of the cost and morbidity associated with breast-conservation surgery, an imaging method that can accurately identify patients who may not require adjuvant radiotherapy could have a significant impact on breast-conservation treatment. The discovery therefore of other microscopic areas of involvement by means of MR imaging may or may not provide a basis for different management and thus might simply add to the cost of overall treatment if all patients treated with conservative surgery continue to receive radiation therapy. This conclusion should be tempered by two considerations. First, the discovery of a second cancer on MR imaging that is not microscopic but may be greater than a size that conventional radiotherapy cannot eradicate and is not detected by mammography may indeed change management decisions. Second, if more than 50% of patients are being treated with adjuvant radiation therapy for microscopic disease, which is only presumed (based on mastectomy studies), than a "negative MR image" for multicentric disease might obviate the need for adjuvant radiation therapy. MR imaging may therefore be useful in randomising patients into suitable trials evaluating the possibility for the safe omission of adjuvant radiotherapy in selected patients.

While a number of predictive factors have been contested, an accurate ability to distinguish those patients who, after being treated with conservative therapy, will develop recurrent disease is lacking. Thus, the possible discovery of other microscopic lesions by MR imaging criteria, even if treatment is unchanged, may offer an investigatory approach to deciding which patients are at greater or lesser risk for developing recurrent disease. These studies would help ascertain the clinical significance of these additional tumour foci which currently is a subject of considerable debate.
12.1.2 Implications for assessing prognosis

A number of studies have shown a statistically significant correlation between the rate of initial contrast-enhancement and microvessel density in malignant tumours (Frouge et al, 1994; Hulka et al, 1995; Baudu et al, 1996). The results of these studies suggest that MR imaging may be useful for the non-invasive assessment of tumour angiogenesis which is a known independent prognostic marker of breast cancer (Weidner et al, 1992). However, these studies have involved analysis of a single section of the tumour only. Further studies correlating the enhancement pattern of the whole tumour with the method of serial sectioned pathological analysis as detailed in this thesis would provide a more objective assessment on the role of MR in the noninvasive assessment of tumour angiogenesis.

The preliminary data in this thesis indicate a high sensitivity of contrast-enhanced MR in demonstrating axillary node metastases but a poor correlation with the number of involved nodes seen histologically. Further developments in breast coils, or coils specifically designed for the axilla may potentially allow a more accurate staging of the axilla.

12.1.3 Assessment of local recurrence in the irradiated conserved breast

In the present study, patients with a high clinical suspicion of local recurrence within the conserved breast were found to benefit from MR imaging. Studies evaluating other patient groups that may similarly benefit from MR imaging need to be undertaken. These may include patients at a high risk of local recurrence based on histological assessment of the primary tumour, and other factors discussed in chapter 3 of this thesis. Studies evaluating MR imaging as a routine follow up investigation in all patients treated with breast-conservation therapy need to be undertaken once dedicated breast MR scanners become available with cost comparable to X-ray mammography.

12.1.4 Assessment of response to neoadjuvant therapy

In the study detailed in chapter 7 of this thesis, preliminary results show that contrast-enhanced MR can accurately define the extent of residual disease following neoadjuvant therapy, findings which have also been supported by other recent studies as well (Abrahams et al, 1996). In these studies, MR imaging was performed at the end of neoadjuvant therapy. However, it may prove possible to use MR imaging in identifying patients who may or may not be responding to therapy early on in the course of neoadjuvant treatment. This would require studies correlating changes in contrast-enhancement pattern and pharmacokinetics during treatment with image guided core biopsies. By identifying patients who do not show any response early on in the course of neoadjuvant treatment, decisions regarding a change in the chemotherapy regimen or
early surgery may be undertaken. MR imaging would also be useful in identifying patients with complete pathological response as this might avoid the need for any surgery.

12.2 MR IMAGING OF ILP IN BREAST CANCER

The findings in this thesis that MR imaging can accurately show residual tumour following ILP makes possible the use of repeat ILP treatment to ensure complete tumour ablation. In the present studies, this was not attempted as the aim was to correlate the residual contrast-enhancement with histological findings. In the next phase of the study, complete tumour ablation should be attempted by repeat ILP treatment if necessary. This would enable us to see how effectively we can use the information obtained from MR images in planning a second ILP treatment. ILP is a safe treatment without any known cumulative toxicity and can therefore be repeated if necessary.

The clinical success of ILP is dependent upon how confidently we can rely on contrast-enhanced MR images in confirming complete tumour ablation. Accurate assessment of residual enhancement may occasionally necessitate subtraction imaging. This is illustrated in chapter 8 by a case treated with a single fibre where near complete tumour ablation was achieved, and the residual 1mm tumour could just be identified on the post-treatment images. The high signal fat on the edges of the treated lesion on T1W FLASH images can obscure such minute areas of enhancement. In another patient detailed in chapter 10 and treated with four fibres, the post-treatment MR images showed increased signal intensity on both the unenhanced and contrast-enhanced MR images, findings which required subtraction imaging to show residual enhancement.

There are potentially two possible ways of confirming complete tumour ablation on MR imaging. Firstly, provided the non-enhancing zone on the post-treatment images measures greater than the enhancing tumour on the pre-treatment images, it can be assumed that complete tumour ablation has been achieved. Methods of superimposing pre-treatment and post-treatment images on each other with the aim of accurate mapping would help in confirming complete tumour ablation. However, it must be appreciated that the patients' breast position within the breast coil in the two scan examination (pre- and post-treatment) is not the same. In order to overcome the latter problem, the tumour site could be marked with MR visible markers and left in position until the post-treatment images have been obtained.

The second method of confirming complete tumour ablation would require the complete absence of abnormal contrast-enhancement on the contrast-enhanced MR images performed after treatment. This can however be difficult particularly in cases where the post-treatment MR images show an enhancing rim after treatment as illustrated in 2 cases discussed in chapter 9. Rim enhancement may be due to inflammatory response, tissue
oedema, neovascularisation or residual tumour at the margins of the zone of laser induced necrosis. All tissue changes other than residual tumour will resolve some days after treatment. In the present studies, MR images obtained 48 h or more after ILP with multiple fibres were able to accurately show the residual untreated tumour. Histological examination in these tumours showed the residual tumour with minimal tissue changes at the margins of the zone of laser induced necrosis. MR guided biopsy of the enhancing rim would be technically difficulty and also mean further invasive investigation. Dynamic imaging to evaluate the pharmacokinetics of contrast-enhancement within the enhancing rim would not be helpful because even if this represents an inflammatory process, the rate of enhancement is likely to be as rapid. Thus, it is best to delay post-treatment imaging at least until 48 h after treatment. The relatively small number of patients studied in this thesis on which this guideline is being made stress the need for further studies evaluating the optimal time interval of obtaining post-treatment scans particularly in tumours treated with multiple fibres in whom complete ablation has been attempted.

The multiplanar capabilities of MR imaging enables the entire tumour to be inspected on serial sections. However, developments in software technology allowing a 3D volumetric reconstruction including maximal intensity projections of the treated tumour will enable the surgeon and radiologist to view the tumour from all directions and accurately ascertain that there are no further islands of residual contrast-enhancement.

Once a confident diagnosis of complete tumour ablation is possible on post-treatment MR images, ethical approval to treat and leave the necrosed tumour in-situ for a longer period of time e.g. 6 - 8 weeks prior to surgical excision would be required. In this group of patients, a repeat MR scan just before surgical resection would be valuable in showing the enhancement pattern of laser treated tumour. Suitable patient groups would need to be identified in whom such an approach of treating and leaving the tumour for a longer period of time would be possible without any harmful effect including delay in starting adjuvant treatment. The results of this study would also provide useful data on the healing of laser treated malignant breast lumps.

In the study evaluating dynamic or real-time MR imaging of ILP in breast cancer, a close correlation was found between the signal loss seen on imaging at the end of ILP and histological extent of tissue necrosis. This finding opens the way for further clinical studies to be undertaken with the next generation of open configuration magnets. The latter magnet design provides the advantage of improved patient access. This will enable accurate needle positioning, insertion of laser fibres and patient monitoring during treatment. In the present studies, the failure to achieve therapeutic effect within the tumour in 50% of patients treated within the bore of a conventional body scanner including the complications of skin and pectoralis burn was related primarily to poor patient access.
In the present study, a subset of patients treated with ILP within the bore of the scanner, underwent contrast-enhanced MR imaging just before ILP treatment. This proved useful in defining the tumour margins at the start of treatment, improved visualisation of the evolving signal loss and allowed accurate visual subtraction of the final extent of signal loss from the area of contrast-enhancement on the pre-treatment images as both images are acquired with the patient's breast in the same position. Further advantage of such an approach is that both the pre-treatment scan for staging the extent of disease and ILP treatment can be performed at one patient visit and examination within the scanner. Developments in MR software technology allowing volume calculations of the evolving zone of signal loss, such that once the desired volume of coagulative necrosis is achieved or if the signal loss is approaching important structure the laser can automatically be switched off would be useful.

Further research on improving MR compatible needles is required as those presently available are associated with marked artefact on MR images. This causes problems not only in monitoring interventional therapies but also during biopsy of small enhancing foci. Recent developments may make the commercial availability of MR compatible needles that do not generate such huge artefacts. One such needle known as the Brookes needle is being developed and tested in the Middlesex Hospital (Hall-Craggs and Mumtaz, 1997). This may have the potential for accurate MR guided biopsy and needle positioning into small enhancing zones.

12.3 FUTURE DIRECTIONS FOR ILP IN BREAST CANCER

ILP of breast tumours avoids the need for general anaesthesia, hospital admission, the cosmetic defect from a surgical scar and is aimed at preserving the size and shape of the breast. In the preliminary study undertaken in this thesis, the cosmetic results after ILP of fibroadenomas appeared to be better than surgical excision. In all patients with fibroadenoma treated with ILP, the size and shape of the breast was preserved. The single complication of skin burn seen in this group healed with a small scar (<1cm in size). Presently, all patients with breast cancer treated with ILP have undergone definitive surgery, but it is likely that similar cosmetic advantages would be obtained in these patients as those seen with the ILP of fibroadenomas. Long term follow up of patients with fibroadenomas treated with ILP would also provide important data on how malignant lumps are likely to heal.

Patients with breast cancer suitable for breast-conservation surgery may also be suitable for ILP treatment. These group of patients are summarised in chapter 3. In addition, ILP may also potentially extend the range of patients suitable for breast-conservation treatment. ILP can be used in patients with two discrete tumours present in separate breast
quadrants. Patients with central tumours without nipple involvement as shown on MR imaging may also benefit from ILP, as these patients may potentially require a mastectomy. Another group of patients that might benefit from ILP are the elderly patient unfit for surgery in whom ILP may be used in combination with adjuvant hormonal therapy.

Based on the experience of ILP in breast cancer to date, it seems that it may be best suitable for treating small cancers, preferably less than 2cm in maximum diameter. Small sized tumours can effectively be ablated using multiple fibres and pull-back techniques. Secondly, by treating small sized tumours, the volume of laser induced necrosis produced and hence the volume of fibrosis secondary to healing would be minimised. This is important as the presence of a palpable nodule in a patient at varying intervals after ILP would raise constant cause of concern.

Although the use of multiple fibres can increase the effective diameter of laser induced necrosis, they need to be carefully positioned in order to avoid complications of skin and pectoralis burn. Methods by which the fibre-tip separation distance can be kept constant within the tumour and prevent fibres from slipping out too superficially during treatment are needed to prevent complications particularly in cases where the treatments are performed within the MR scanner. As discussed earlier in chapter 9, it may be safer to treat the relatively superficial tumours with fewer fibres and repeat treatments if necessary. In the present study, the number of fibres used were roughly matched to the size of the tumour being treated. A more accurate way of deciding on the number of fibres to be used based on actual tumour volume measured on imaging will improve the number of tumours that can safely be ablated completely.

Finally, several other minimally invasive techniques as detailed in chapter 3 have been described in the treatment of solid tumours. Although no detailed clinical or experimental studies on the efficacy of these treatments in breast tumours have been published, some techniques particularly bipolar radiofrequency thermal ablation may offer a more cost-effective approach in the treatment of breast tumours compared with ILP.

12.4 FUTURE DIRECTIONS FOR ILP IN FIBROADENOMAS

In chapter 11 of this thesis, preliminary data on the application of ILP for the treatment of benign breast fibroadenomas was presented. The stimulus for this study was based on the encouraging results of ILP in breast cancer in creating clinically useful thermal necrosis. In all patients in this series, there was a reduction in size of the fibroadenoma in the first few weeks after ILP treatment. The satisfactory response to ILP treatment led 10 patients to opt for continued conservative treatment instead of surgical excision. Further experience in the ILP of fibroadenomas in a larger series of patients and comparison with
age matched patients treated surgically and non-surgically would provide data on the actual benefits of ILP in the treatment of fibroadenomas.

In the present study, ultrasound was useful in monitoring the size reduction of the laser treated fibroadenoma at follow-up but not in showing the extent of necrosis or residual tumour. Difficulty in ultrasonographic assessment was seen in one patient possibly due to capsular destruction following ILP. MR imaging was useful in defining the extent of necrosis only in situations where the tumour enhanced before treatment. A complimentary clinical and imaging assessment is therefore required in the follow up of these patients.

MR imaging may be useful in monitoring of ILP of breast fibroadenomas with the availability of open access MR scanners. This will enable the treatment to be performed at single hospital visit, and further follow up can be then undertaken using ultrasonography. Contrast-enhanced Ultrasound may prove a useful imaging technique comparable with MR imaging in defining the extent of necrosis and monitoring size reduction of the treated fibroadenoma.
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1. Breast Surgery after neoadjuvant treatment. Is it Necessary


Hall-Craggs MA, Mumtaz H
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6. Staging of symptomatic primary breast cancer with magnetic resonance imaging
Mumtaz H, Hall-Craggs MA, T Davidson, Walmsley K, Thurell W, Taylor I.


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2. The potential role of interstitial laser photocoagulation for the treatment of breast fibroadenoma.  
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Breast surgery after neoadjuvant treatment. Is it necessary?

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The optimum management of women with advanced loco-regional breast cancer (T_{2-4}, N_{1-3}) is controversial. Neoadjuvant therapy in the form of chemotherapy and or radiotherapy is popular and results in an encouraging local response in over 70% of patients. However, should subsequent surgery (either mastectomy or breast conservation treatment) be undertaken in women who respond?

We present a prospective evaluation of 15 patients with T_{2-4}, N_{1-3} tumours (including 1 bilateral cancer) who underwent mastectomy after achieving a complete clinical response to neoadjuvant treatment. All patients had 6 cycles of chemotherapy and 10 also received 50 Gy radiotherapy. In addition to clinical examination, the response to neoadjuvant treatment was assessed by mammography (in all cases) and by magnetic resonance imaging (MR) (in eight patients). Careful histopathological assessment of the mastectomy was undertaken to determine the extent of residual disease.

In all patients histological malignancy was recognized within the breast. The size varied from 0.6 to 6.5 cm in maximum diameter with three grade I, eight grade II and five grade III tumours. Axillary lymph nodes were positive in seven patients. In conclusion, surgery is indicated for control of residual disease in locally advanced breast cancer regardless of the response to neoadjuvant treatment. Our preliminary observations suggest a potential role for breast MR in defining the extent of residual disease which may aid in the planning of surgery.

Key words: breast cancer; chemotherapy; mastectomy; magnetic resonance imaging.

Introduction

The incidence of locally advanced breast cancer has decreased in the West as a result of enhanced public awareness and the increased use of screening mammography compared with developing countries where it still accounts for up to 20–30% of newly diagnosed breast cancer.\(^1\) The last two decades have confirmed the contribution of adjuvant systemic treatment in the primary management of breast cancer.\(^2\) Primary chemotherapy is the initial treatment of choice for patients with locally advanced tumours and results in substantial tumour shrinkage and downstaging in almost 70% of patients.\(^1,3\) However, what the optimal sequence of subsequent treatment should be, or whether one or two local treatments are necessary is still controversial. In different studies, surgery or radiotherapy alone\(^4\) or a combination of the two\(^5\) have been used following primary chemotherapy. Although these studies have not demonstrated a survival advantage, surgical removal of the primary with axillary dissection appears superior to radiation therapy in the achievement of long-term local control.

The requirement for further treatment is based on the assumption that residual disease is present despite primary chemotherapy. The dilemma in the management of the breast after neoadjuvant treatment is in defining the extent of residual disease so that appropriate surgery may be undertaken. Previous studies have shown the possibility of performing breast conservation surgery following neoadjuvant treatment\(^5\) but have used methods of limited sensitivity in defining the extent of residual disease and have included in their analysis patients with small-sized tumours (range: 3–5 cm).

The aim of this study was to assess prospectively the extent of residual disease in mastectomy specimens following neoadjuvant treatment of locally advanced breast cancer (T_{3-4}, N_{1-2}). In addition we present our preliminary findings of the role of magnetic resonance (MR) imaging, compared with mammography, in the management of locally advanced breast cancer.

Patients and methods

Over a period of 1 year, 15 patients with a median age of 50 years (range: 28–55) presented with locally advanced breast cancer (T_{3-4}, N_{1-2}) and were prospectively evaluated. Of these, nine patients were pre-menopausal and six post-menopausal. There were 14 unilateral and one bilateral breast cancer. All patients received neoadjuvant...
chemotherapy comprising 6 cycles of CMF (cyclophosphamide, methotrexate, 5-fluorouracil) at a dose of 600, 40, and 600 mg/m² respectively on days 1 and 8, with a cycle length of 21 days. Radiotherapy was given to 10 of the 15 patients, at the end of the last cycle of chemotherapy at a total dose of 50 Gy given in 25 fractions. Radiotherapy was limited to the breast, internal mammary nodes and the supraclavicular region.

The median tumour diameter at the start of treatment was 6 cm (range: 5-10) with all patients having palpable axillary lymph nodes. Pre-treatment mammography and fine needle aspiration cytology was performed in all patients. In addition 'trucut' tissue biopsy was carried out in seven patients and oestrogen receptor status evaluated. Following the final chemotherapy cycle or radiotherapy session, all patients were evaluated both clinically and mammographically. Magnetic resonance imaging was also performed in three patients at the start of treatment and in eight patients post-treatment. Complete staging in the form of chest X-ray, liver ultrasound and bone scan were performed in all patients at the beginning and end of the neoadjuvant treatment. Patients with distant metastases were excluded from the study.

Breast MR was performed using a dedicated receive-only double breast coil on a 1 Tesla scanner (Magnetron 42SP, Siemens, Erlangen, Germany). A T1-weighted 3-dimensional fast low angle shot (FLASH) sequence (TR 18 ms, TE 7 ms, FA 40 degrees, 128 x 256 matrix, 64 partitions, effective slice thickness 2 mm) was made before and after enhancement with Gadolinium diethylenetriamine pentaacetic acid (Gd-DTPA) (Magnevist, Schering UK) at a dose of 0.1 mmol/kg body weight.

Following neoadjuvant treatment, patients were jointly assessed by a surgeon and clinical oncologist. All patients were fully informed and consented to mastectomy with full axillary node clearance. Following resection, the specimen was delivered fresh to the pathology laboratory. All specimens were carefully analysed by a dedicated breast histopathologist. The mastectomy specimen was serially sliced in the transverse plane relative to the patient. These slices were compared to the area of MR abnormality and the craniocaudal view of the mammograms. Blocks were taken from the tumour where it was visible macroscopically, or from the presumed site of the tumour which appeared as a greyish mottled area with a rather firm texture.

Random blocks from the breast including all the resection margins were also taken. Sections were cut at 3-4 μm, stained with haematoxylin and eosin and mounted using standard techniques. The following histological features were noted: maximum tumour size, presence of a focal mass or a more diffuse pattern, type and grade of the tumour. In situations where no residual tumour was initially identified, further search was undertaken using the mammogram or breast MR as a guide.

Results

The results of clinical, mammography, MR imaging and histopathological analysis are summarized in Table 1. In 11 breasts, the tumour boundaries were no longer measurable, although the breast was diffusely indurated at the site of initial tumour. In the other five breasts, an ill-defined lump was palpable in one quadrant.

Macroscopic examination of the mastectomy slices confirmed visible tumour in six breasts only, of which five were clinically palpable. Residual microscopic disease was confirmed in all 16 mastectomy specimens. This was present as a focal mass in six specimens and allowed an accurate estimation of the residual tumour diameter. In the other 10 specimens, residual disease was more diffuse and interspersed within areas of normal and necrotic/fibrosed breast parenchyma and extending to the pre-treatment tumour margins. Accurate estimation of residual tumour size was not possible in these patients, and was taken as the area between positive margins. The median tumour diameter was 2.0 cm (range: 0.6-6.5). Thus all but two of the tumours were successfully downstaged from T_{1a} to T_{2-3}. Residual tumours were infiltrating ductal carcinoma (n = 10), invasive plus ductal carcinoma in situ (n = 4) and pure ductal carcinoma in situ (n = 2). The histological grade of the residual tumour was grade 1 in three, grade II in eight and grade III in five patients. Axillary nodes were positive in seven patients.

In all specimens, extensive chemoradiotherapy-induced fibrosis and tumour necrosis was evident. The median diameter of the residual tumour in the five patients treated with chemotherapy only was 24 mm (range: 19-60) and that of patients treated with combined chemotherapy and radiotherapy was 18 mm (range: 6-45). In three of the 11 breasts treated with combined chemotherapy and radiotherapy, the resected specimens had residual tumour less than 10 mm in size. Of these, one patient had a 6 mm area of scattered cancer cells of doubtful viability. In one patient, on initial tissue sampling, only pagetoid spread of cancer cells within the ducts was noted with no evidence of invasive tumour. However on subsequent histological analysis, a 6-mm invasive tumour was detected underneath the nipple. In two patients, residual tumour was completely in situ with no evidence of invasive foci.

Post-neoadjuvant mammography illustrated a definite reduction in tumour size in 10 of the 16 breasts. This was shown as a reduction in the extent of microcalcifications (n = 3), decreased size and density of the spiculated mass (n = 4) and decreased parenchymal density (n = 3) (Fig. 1). Of the six remaining patients, in three there was no change in the mammographic appearances post-treatment. In the remaining three patients, the pre-treatment mammograms were not diagnostic of breast cancer and showed no new changes following treatment. Mammographic features of decreased density tended to overestimate the size of residual tumour while the area of microcalcifications or spiculated mass was smaller than the histological size of the tumour.

Breast MR was performed in three patients at the start of treatment and illustrated the large enhancing mass and enhancing axillary lymph nodes consistent with locally advanced breast cancer. Post-treatment MR scans were performed in eight patients. This showed diffuse enhancement in two patients (Fig. 1), a unifocal enhancing mass in three (Fig. 2), multifocal in one, combined focal with diffuse enhancement in one and no contrast enhancement in one. In the latter patient, histopathological examination...
<table>
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<th>Post-treatment mammography</th>
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<th>Microscopic examination</th>
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<td>slight reduction in tumour size; extensive diffuse enhancement in lateral half of breast</td>
<td>40 mm firm, indurated tumour in outer quadrant</td>
<td>Extensive area of DCIS, no invasive foci, max dimension ~ 50 mm</td>
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<td>36</td>
<td>no residual lump</td>
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<td>2 foci of invasive cancer with DCIS separated by areas of fibrosis and necrosis. Max dimension ~ 18 mm</td>
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<td>20 mm central firm grey area</td>
<td>65 mm, idc multiple areas of intratumoral necrosis, grade 3, node + ve fibrous tissue infiltrated by adenocarcinoma cells in cords and small groups: max dimension ~ 17 mm, grade 2, node + ve 8 mm, idc; grade 2, node + ve</td>
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<td>47</td>
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<td>C</td>
<td>40 mm spiculated mass, no change in mammographic size</td>
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<td>60 mm firm tumour</td>
<td>19 mm idc, grade 2 tumour extends to deep resection margin 7 nodes + ve, 2 nodes in supravacuicular fossa</td>
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<td>49</td>
<td>no lump</td>
<td>C+XRT</td>
<td>30 mm area of microcalcification (no change in mammographic size)</td>
<td>not done</td>
<td>central greyish mottled area</td>
<td>19 mm idc, grade 2, node + ve</td>
</tr>
<tr>
<td>50</td>
<td>vague thickening</td>
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<td>indeterminate mammogram (pre and post-treatment) decreased mammographic density</td>
<td>10 mm area of focal enhancement</td>
<td>no tumour, indurated area mottled yellow and brown</td>
<td>multiple areas of residual DCIS, max dimension ~ 30 mm, node + ve</td>
</tr>
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<td>50</td>
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<td>multiple areas of residual DCIS, max dimension ~ 30 mm, node + ve</td>
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<td>52</td>
<td>30 mm residual lump (1 quadrant)</td>
<td>C</td>
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<td>18 mm central enhancing mass with tenting of Pectoralis major, node + ve</td>
<td>20 mm central tumour</td>
<td>24 mm idc, grade 2, node + ve</td>
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<td>52</td>
<td>25 mm residual lump (1 quadrant)</td>
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<td>decreased mammographic density</td>
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<td>20 mm firm spiculated area</td>
<td>23 mm, idc, grade 3, 1 node + ve</td>
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<td>53</td>
<td>30 mm central residual lump</td>
<td>C</td>
<td>20 mm residual spiculated mass + microcalcification</td>
<td>25 mm focal enhancement, node + ve</td>
<td>30 mm grey mottled area</td>
<td>24 mm idc, grade 2, node + ve</td>
</tr>
<tr>
<td>53</td>
<td>vague thickening &amp; nodularity</td>
<td>C</td>
<td>indeterminate (pre and post-treatment)</td>
<td>24 mm focal enhancement with background diffuse patchy enhancement</td>
<td>no tumour</td>
<td>20 mm idc, with associated DCIS, grade 2, node + ve</td>
</tr>
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</table>
viability within a fibrous stroma. A focally enhancing mass
carcinoma presence of diffuse enhancement correlated to ductal
correlated histologically to an invasive cancer and the

showed a 6-mm area of scattered cancer cells of doubtful viability within a fibrous stroma. A focally enhancing mass correlated histologically to an invasive cancer and the presence of diffuse enhancement correlated to ductal carcinoma in situ. Non-enhancing areas within the main enhancing mass correlated to the presence of intratumoral necrosis in all cases. The extent of contrast enhancement on breast MR correlated closely with the extent of residual tumour seen on histopathological analysis.

Discussion

The need for subsequent surgery following neoadjuvant treatment in locally advanced breast cancer is still controversial with opinions ranging from no additional surgery in patients with complete clinical remission to either breast conservation surgery or total mastectomy with axillary clearance.

This study confirms several important aspects of neoadjuvant treatment. First, using conventional chemotherapy nearly all patients are successfully downstaged. Second, clinical examination is not accurate for estimating the extent of residual disease. This was evident in our study that 11 of the 16 breasts showed generalized vague thickening with no clinically palpable lump. In addition, in patients with clinically palpable lump, residual disease extended beyond the margins of the lump. Third, compared with mammography, magnetic resonance imaging provided a more accurate assessment of the extent of residual disease. Finally, on microscopic examination residual disease was not present as a single focus of carcinoma, but rather as islands of viable tumour cells interspersed within fibrous breast stroma, with tumour deposits present at the original resection margin.

With conventional chemotherapy regimes the reported complete clinical remission (CR) rate ranges from 15–28% in patients with an initial tumour diameter greater than 3 cm.\textsuperscript{10,11} More recently a much higher CR rate of 66% has been reported with the use of long-term infusional chemotherapy regime comprising epirubicin, cisplatin and fluorouracil.\textsuperscript{11} However the pathological CR in patients undergoing surgery was 27% suggesting a poor correlation between clinical and pathological CR. The addition of pre-operative radiotherapy to chemotherapy has shown to improve further pathological response and CR rate.\textsuperscript{6} The results in our series support this observation with three of the 10 patients treated with combined neoadjuvant treatment having residual tumour less than 10 mm in maximum diameter. However, no statistical conclusion comparing the response to chemotherapy alone with the use of combined chemotherapy and radiotherapy in this study can be made in view of the relatively small number of patients studied.

Breast cancer is not an encapsulated tumour, and does not shrink centripetally in response to chemotherapy. Thus, although the tumour may be downgraded clinically it may not have been downgraded histologically. Residual microscopic disease may still be present at the original macroscopic margins as was evident in the mastectomy specimens analysed in this study. Other studies have also confirmed that clinical evaluation of response to chemotherapy is less accurate than pathological assessment of response.\textsuperscript{13} Achievement of specimens free of residual macroscopic tumour after pre-operative chemotherapy is an excellent prognostic factor for prolonged disease-free and overall survival. In addition surgical axillary node staging is an important component of treatment following pre-operative chemotherapy and is a significant independent prognostic variable.\textsuperscript{14}

Accurate estimation of tumour size in the operating room is difficult as the previously firm tumour loses its consistency following destruction of a significant part of the tumour mass or may only be present as scattered islands of degenerate and viable tumour cells. Some workers have therefore suggested marking the original tumour margins at the start of treatment as this would aid in locating the part to be removed.\textsuperscript{15} In addition they have suggested the use of frozen-section biopsies of the resection margins to check for the presence of microscopic foci of residual cancer. If involved, further excision is advised until the margins are not infiltrated with malignant cells. However, this technique is difficult and time-consuming.

Examination of mastectomy specimens in previous retrospective studies suggests that only 23–42.5% of patients may have been suitable for breast conservation surgery\textsuperscript{16–18} with residual disease being present in over 90% of specimens examined.\textsuperscript{16–18} Other studies\textsuperscript{5} have reported a much higher breast conservation rate approaching 95% although only a small percentage of patients with locally advanced breast cancer (T_{4A}) were included. Thus for accurate surgical planning, an imaging technique with a high sensitivity in detecting residual disease is of critical importance.

Chemotherapy-induced fibrosis has been shown to impair evaluation of residual tumour by means of clinical
Fig. 1. Images of 50-year-old woman with T3N1 carcinoma of the right breast. The pre-treatment cranocaudal mammogram (a) shows generalized increased density of the breast parenchyma and post-treatment mammography (b) shows generalized reduction in the parenchymal density more marked in the lower quadrant. Pre-contrast (c) and post-contrast (d) T1-weighted MR images showed multifocal areas of diffuse enhancement (curved arrows) which correlated accurately with multifocal area of ductal carcinoma in situ with no invasive component found following mastectomy. Note the central position of the residual tumour involving two quadrants.

examination, mammography and/or ultrasound.20,21 Several recent studies have shown improved sensitivity of breast MR compared with mammography in the diagnosis of breast cancer.22 In the assessment of response to neoadjuvant treatment, Gilles et al.,23 using contrast-enhanced subtraction MR imaging, identified residual disease in 17 of the 18 patients undergoing neoadjuvant treatment whereas mammography showed residual disease in only nine of 14 patients. In addition the extent of residual disease on MR correlated closely with histological analysis.
Our preliminary experience confirms this potential role of breast MR. In this series, MR images provided an accurate estimation of the extent of residual disease in all patients. In one patient, with a 6 mm area of residual cancer cells but of doubtful viability, post-treatment MR images confirmed no signs of residual disease. In retrospect, surgery could have been avoided in this patient and complete remission achieved with an additional boost dose of radiotherapy to the breast. It is therefore likely that breast MR may aid in the diagnosis of complete clinical remission which would correlate more accurately with pathological remission. This will allow in the selection of patients that may not require any additional surgery or in the planning of breast conservation surgery, which will eventually translate to reduced local recurrence rates.

Thus, with currently available conventional neoadjuvant regimes and imaging techniques, we caution against the use of any surgery less than a total mastectomy if optimal local control is to be achieved. However, it is likely that with the introduction of more aggressive chemotherapeutic regimes and magnetic resonance imaging safe preservation of the breast might be achieved.

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Accepted for publication 19 April 1996
C-myc oncogene expression in human melanoma and its relationship with tumour antigenicity

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Melanoma produces specific tumour antigens which are capable of eliciting an immune response. However, this tumour evades the immune system, in part, by downregulation of class I HLA antigens on the cell surface, which are required for T cell recognition. It has been suggested that the oncogene c-myc may have a role in effecting this change in vitro, however, the relationship between oncogene level and tumour antigenicity has not been established in human tumours. This study measured c-myc oncprotein in 94 melanoma specimens (46 primary tumours and 48 regional metastases) using flow cytometry and evaluated class I HLA expression with immunohistochemistry. C-myc expression was found in 91 tumours (96%) with higher expression in metastases than primary melanomas (P<0.005). Class I HLA expression was found to show great variation although metastases showed less antigenicity than primary tumours (P<0.01). Analysis of the relationship between these two parameters revealed a highly significant correlation in both primary (P<0.01) and metastatic disease (P<0.01), with high oncprotein being associated with down regulation of cell surface antigens. Knowledge of the control of tumour antigenicity is likely to provide an objective platform for the development of new strategies for immunotherapy.

Key words: melanoma; antigen; oncogene.

Introduction

HLA class I antigens are heterodimers composed of a polymorphic heavy chain glycoprotein, non-covalently associated with a β2 microglobulin subunit. The heavy chains are integral transmembrane structures consisting of three extracellular domains linked by a hydrophobic transmembrane segment to the intracellular cytoplasmic domain. The light chain β2 microglobulin has no transmembrane region and is kept on the cell surface by virtue of the non-covalent association with the extracellular domains of the heavy chain. Class I HLA antigens are expressed on all nucleated cells of the body, and also on platelets. They play a crucial role in immune recognition by CD8-positive cytotoxic T lymphocytes which are only capable of detecting antigens presented on the cell surface in association with class I HLA.

Melanoma expresses a number of 'tumour antigens' including Melanoma Associated Antigen (MAGE I-III) and Gangliosides (e.g. GM3) which are capable of eliciting a specific immune response. The majority of tumour antigens are not completely specific to malignancy but are present in very low concentrations in normal host tissues such that during thymic development lymphocytes with a high affinity to these epitopes were eliminated. Thus low affinity lymphocytes remain and exist in the mature adult but autoimmunity does not occur as the antigen is insufficient to effect clonal expansion. In the presence of malignant transformation, expression of these antigens is often greatly increased to the level where an immune response can be elicited if the epitope is presented in appropriate fashion. The presence of class I HLA on the tumour cell surface is therefore crucial to the effector arm of this immune response.

It has been observed in melanoma and many other human malignancies that tumour cells show a considerable reduction in the expression of class I HLA antigens. This allows the tumour cells to evade immune attack by CD8-positive T lymphocytes despite the presence of immunogenic molecules on the cell surface. In metastatic disease the degree of class I HLA downregulation has been shown to be of prognostic significance.

It has been suggested that one possible explanation for this phenomenon is related to oncogene activity. In a study using melanoma cell lines class I HLA expression was found to correlate inversely with the c-myc level suggesting that the oncogene may cause downregulation. This was supported by the finding that transfection of c-myc caused a reduction in class I HLA antigen level in cells that previously expressed low levels of the oncogene. Recently, further interest has focused on the activity of c-myc in melanoma following a study suggesting that the level of c-myc expression correlates with a poor prognosis. To date the relationship between c-myc and class I HLA expression has not been established enough in human tumour samples to investigate this as a
Laser Therapy for Breast Cancer: MR Imaging and Histopathologic Correlation

PURPOSE: To investigate magnetic resonance (MR) imaging guidance of interstitial laser photocoagulation to treat primary breast cancer.

MATERIALS AND METHODS: Twenty female patients with symptomatic breast cancers diagnosed at cytologic examination underwent interstitial laser photocoagulation by means of a single fiber prior to surgical excision. Gadolinium-enhanced T1-weighted three-dimensional fast low-angle shot (FLASH) MR imaging was performed before and after laser therapy (median, 48 hours; range, 24–96 hours). Following resection, tumors were mapped in detail histopathologically. The extent of disease, size of laser burn, and extent of residual tumor were correlated with MR findings.

RESULTS: Twenty-seven tumors were detected at histopathologic examination in the 20 patients. Five patients had more than one invasive mass. Twenty-five of the 27 tumors were identified as discrete enhancing masses at MR. The two missed invasive foci were obscured on MR images by diffuse patchy enhancement that correlated with the presence of an associated extensive intraductal component. Early (4-hour) follow-up images failed to depict the laser effect. Later (24–96 hours) follow-up images depicted the laser-induced necrosis as a zone of nonenhancement within the residual enhancing tumor. The correlation coefficients (MR vs histopathologic analysis) for the laser-burn diameter and residual tumor were 0.80 and 0.86, respectively.

CONCLUSION: Delayed gadolinium-enhanced MR images can help define the extent of laser-induced necrosis and residual tumor after interstitial laser photocoagulation therapy in breast cancer.

Breast cancer is the most frequently observed cancer among women and has the highest incidence of any cancer in western Europe and North America. Worldwide, more than 1 million women per year will develop breast cancer by the year 2000 (1). Recent trends in the management of breast cancer have moved toward breast conservation, the safety of which has been validated in several prospective randomized trials that have found no differences in disease-free interval and overall survival in patients who have been treated with breast conservation rather than mastectomy (2).

In the majority of women with disease suitable for this treatment, conservative breast surgery produces a more acceptable cosmetic appearance than mastectomy, preserves the patient’s body image, and allows increased freedom of dress (3). Minimally invasive therapeutic procedures have been developed to reduce surgical trauma by exposing and isolating the smallest possible segment of the anatomy that still allows access to the target volume with minimal injury. Such procedures necessitate shorter hospitalization and offer potential cost savings. This concept combined with the known safety of breast conservation has prompted research into the application of minimally invasive therapies to breast cancer.

Interstitial laser photocoagulation was first reported in 1983, to our knowledge, as a minimally invasive therapy to provide localized tumor destruction in solid organs (4). Tumors are destroyed as a result of direct heating with low-power laser light energy delivered via thin optical fibers. The size and shape of thermal lesions are difficult to predict, however, owing to biologic variability (5), fiber tip charring, and changing optical and thermal properties of the tissue during interstitial laser photocoagulation (6). Thus, interstitial laser photocoagulation will be useful clinically only if noninvasive, accurate monitoring methods are developed to assess the extent of heat-induced necrosis. Diagnostic imaging techniques including ultrasound (US), computed tomography (CT), and magnetic resonance (MR) imaging have been investigated as modalities to provide image-based guidance at interstitial laser photocoagulation, the success of which depends on how reliably the images predict the final volume of thermal necrosis.

The application of interstitial laser
photorcoagulation in primary breast cancer prior to definitive surgery was first described in detail, to our know-
edge, by Harries et al (7), who used a semiconductor diode laser. The au-
ths found that US was useful to
guide needle and fiber-tip placement
within the tumor and to help predict
tumor size at the start of therapy but
was grossly inaccurate for measuring
the volume of laser-induced tumor
tissue and the extent of the remain-
ing tumor. This finding was similar to
that observed in the treatment of he-
patitis metastases (8). In this latter
study, US did not help evaluate le-
sion size after interstitial laser pho-
tocoagulation, because areas of coagu-
lative necrosis were thought to have
US characteristics similar to those of
tumor. This similarity between treated
and untreated tumor made subsequent
targeting of residual tumor
difficult and was the main obstacle
to achieving complete tumor abla-
tion.

For interstitial laser photoagula-
tion to have a clinical role in the treat-
ment of primary breast cancer, an
imaging technique is needed that pro-
vides accurate initial local staging of
disease and clear differentiation be-
tween necrotic and residual tumor
after therapy so further treatment
can be given if necessary to achieve com-
plete tumor ablation. Ideally, thermal
changes should be shown in real time
and should accurately predict the fi-
nal extent of necrosis. Of the cur-
rently available breast imaging tech-
niques, contrast material–enhanced
MR imaging appears to be the most
sensitive for tumor detection and
staging (9,10) and offers several ad-
vantages in monitoring laser-tissue
interactions. MR imaging is less op-
erative dependent and has better soft-
tissue contrast resolution than US.
Findings in preliminary experience
with delayed contrast material–en-
hanced CT and MR imaging (7) sug-
gest that MR imaging may be more
accurate for depicting the effect of
interstitial laser photoagulation in
primary breast cancer (n = 5), but to
our knowledge no studies have yet
been performed with these imaging
modalities in real time.

In this study, we evaluated the use
of MR imaging after therapy to mea-
sure the therapeutic effect of intersti-
tial laser photocoagulation in primary
breast cancer prior to surgical resec-
tion. MR findings were correlated
with histopathologic measurements
of the extent of necrosis and residual
tumor induced by interstitial laser
photorcoagulation.

MATERIALS AND METHODS

Twenty patients, aged 34–79 years
(median, 57 years), with breast cancer di-
agnosed at cytologic examination after
fine-needle aspiration of a breast mass,
underwent treatment with interstitial laser
photocoagulation prior to surgical resec-
tion. All patients were recruited from a
breast clinic for symptomatic patients, and
all had a palpable tumor (although this
was not a prerequisite for entry into the
study). All patients gave written informed
consent for participation in this study,
which was approved by the ethical com-
nittees for human research at Middlesex
Hospital, London, England, and Royal Sur-
vey County Hospital, Guildford, England.
The laser used in this study was a semi-
conductor diode laser (Diomed-25; Di-
omed, Cambridge, England), with a wave-
length of 805 nm. One sterilized, freshly
cleaved silica-clad, 400-μm-diameter fiber
with a bare tip was used to deliver laser
energy to the tumor. The tip was pre-
chared by placing a small drop of the pa-
tient’s blood on the fiber tip and firing
the laser briefly at high power (7). The skin at
the site of percutaneous needle insertion
was infiltrated with local anesthetic (1% lidocaine) in all cases. Intravenous analge-
sia (meperidine hydrochloride, 50–100 mg)
was necessary in five patients.

With use of aseptic technique and US
guidance (Aloka 650 [7.5-MHz breast
probe]; Aloka, Tokyo, Japan) an 18-gauge
needle was inserted percutaneously into
the center of the tumor and the prechared
fiber was passed through the needle so
that its bare tip lay 3 mm beyond the needle
and well within the tumor. The lesion was then
treated at low power (2 W/500 sec [1,000 J]).
A single interstitial laser photocoagulation
lesion was made in each patient.

All treatments were monitored with
real-time US, and the maximum extent of
thermal changes (seen as an expanding
zone of increased echogenicity) was mea-
sured. The procedure had to be stopped in
two patients at 300 and 350 seconds, ow-
ing to pain, which resolved as soon as the
laser was switched off. There were no
other complications.

Breast MR Imaging

Technique—MR imaging was performed
on a 1-T imager (Magnetom 42 SP; Sie-
mens, Erlangen, Germany) before and af-
after laser therapy by using a dedicated re-
ceive-only, double breast coil. The patient
was placed prone. An intravenous can-
nula was in place, which obviated moving
the patient or retuning the coil between
sequences. Transverse Tl-weighted three-
dimensional fast low-angle shot (FLASH)
imaging (repetition time msec/echo time
msec = 18/7, 40° flip angle, 128 × 256 ma-
trix, 64 sections acquired, 2-mm effective
section thickness, 110-mm field of view)
was performed before and after enhance-
ment with gadopentetate dimeglumine
(Magnevist; Schering, Berlin, Germany) (0.1
mmol per kilogram of body weight). The
contrast material was injected rapidly,
within 10 seconds, followed by a rapid
bolus of 10 mL of normal saline. Imaging
was commenced immediately after the
injection. Short inversion time inversion-
recovery (STIR) imaging (2,660/30/140 [in-
version time msec], 140° flip angle, 160 ×
252 matrix, 5-mm effective section thick-
ness, 50% section gap) was performed in
all patients before FLASH imaging and
before injection of contrast material.

Interpretation—All MR images were re-
viewed by one radiologist (M.A.H.C.), who
is experienced in breast MR. The presence
was recorded of focal enhancement (de-
finied as an enhancing area with well-de-
}
basis of the clinical and mammographic findings of the extent of disease. The sur-
dian interval of 48 hours after therapy (range, 24-96 hours).
sequent patients were obtained at a me-
were seen on the 4-hour follow-up images obtained after laser therapy were obtained
means of standard manufacturer's soft-
duced necrosis. The maximum transverse
diameter of these zones was measured by
considered to represent areas of laser-in-
therapy, the size (maximum transverse
tumor mass were noted and measured. Any additional areas of
focal enhancement that suggested multifo-
mass were noted. Any additional areas of
diameter) and site of the main enhancing
logic assessment of residual tumor following interstitial laser photocoagulation (excluding
tumors in which the fiber was incorrectly placed).
induced necrosis (including the five tumors in which laser necrosis extended beyond the tu-
mor margin) (H = .80).
ser-treated tumors, in two tumors missed at interstitial laser photocoagulation, and in seven
additional untreated tumors. (c) Correlation between MR and histologic assessment of laser-
therapy, the size (maximum transverse
tumor mass were noted. In patients with central laser necrosis, the size of re-
sidual tumor was obtained by subtracting the maximum transverse diameter of the tumor from the diameter of laser necrosis in the same plane. The residual tumor type, grade, associated ductal carcinoma in situ (DCIS), and estrogen-receptor sta-
tus were evaluated in all patients. The presence of any additional invasive tu-
mors was also recorded. In the last two patients we studied, additional staining with diaphorase was undertaken to de-
donstrate cell life. This method utilizes the reduction of tetrazolium salts by nicotin-
amide adenine dinucleotide phosphate (NADP) diaphorase on frozen-tissue sec-
tions, which produces a water-soluble, intense blue, granular precipitate called di-
formazan (11). The border between blue-stained and unstained devitalized
structures is delineated sharply, which permits an accurate determination of the extent of tissue necrosis.

Statistical Analysis
Linear regression analysis was used to compare the US, MR imaging, and histopa-
opathologic measurements of the primary tumor, laser-induced necrosis, and re-
sidual tumor.

RESULTS
In addition to the 20 clinically pal-
pable tumors, seven additional tumors were detected in the 20 patients at histo-
pathologic examination. Fifteen patients had single tumors, four had two inva-
sive foci in the same breast (only one of which was palpable), and one had bilat-
eral cancer (a single, palpable tu-
mor on one side, which was treated, and three nonpalpable tumors on the other side, which were not treated). In the 16 breasts with single tumors, 13 tumors were infiltrating ductal carci-

Figure 2. (a) Correlation between US and histologic assessment of laser-induced necrosis (r^2 = .30) (n = 20 interstitial laser photocoagulation therapies, including therapy in two patients in whom no changes were seen at US during interstitial laser photocoagulation). (b) Correlation between MR and histopathologic assessment of primary tumor size (r^2 = .90) (n = 22 invasive tumors). Histopathologic assessment of primary tumor size was possible in 13 of the 18 la-
sertreated tumors, in two tumors missed at interstitial laser photocoagulation, and in seven additional untreated tumors. (c) Correlation between MR and histologic assessment of laser-induced necrosis (including the five tumors in which laser necrosis extended beyond the tu-
mor margin) (r^2 = .80) (n = 18 laser-treated tumors). (d) Correlation between MR and histo-
logic assessment of residual tumor following interstitial laser photocoagulation (excluding tumors in which the fiber was incorrectly placed) (r^2 = .86) (n = 18 laser-treated tumors).
nomas and one tumor was mucinous cancer. The multifocal invasive cancers were all infiltrating ductal carcinomas. The presence of extensive DCIS was noted in three of the five breasts with multifocal cancer and in one of the 16 breasts with unifocal tumors.

Macroscopically in the surgical specimens, the laser burn appeared as a white area surrounding a central charred cavity that corresponded to the position of the laser fiber. At the periphery of the white zone was a thin hemorrhagic zone (Fig 1a). The microscopic features (Fig 1b) were consistent and showed three zones. The charred cavity (zone 1) contained necrotic and carbonized debris. This was surrounded by an area of in situ fixation (zone 2), which was characterized by morphologically normal cells but with smeared nuclei that had a featureless, hyperchromatic appearance. The cytoplasm of these cells was hypereosinophilic, consistent with the presence of coagulated proteins. Within the hemorrhagic rim (zone 3), the cells showed less severe damage, with unstained, slightly hyperchromatic nuclei that retained their chromatin pattern and nucleoli. These cells were surrounded by proliferating fibroblasts, blood vessels, and extravasated red blood cells.

In the last two patients studied, NADP-diaphorase staining confirmed that cells in all three zones seen on the hematoxylin-eosin–stained specimen of the laser-induced lesion were necrotic. The extent of necrosis seen with hematoxylin-eosin and NADP-diaphorase staining was the same.

The area of interstitial laser photocoagulation necrosis was completely confined within the tumor margins in 13 patients, extended beyond the margin of the invasive tumor in five, and missed the tumor in two. Accurate estimation of the histologic size of the primary tumor or the extent of laser-induced tumor necrosis was not possible in the five patients in whom the treatment effect extended across the margins of the tumor. In the 22 tumors in which these measurements could be made on the surgical specimen (13 tumors treated with interstitial laser photocoagulation, two that were missed completely at interstitial laser photocoagulation, and seven that were untreated), the median diameter of the invasive tumor was 20 mm (range, 4–33 mm).

US guidance enabled correct positioning of the laser fiber in all but two cases, in which the area of treatment was shown histopathologically to lie outside the tumor, in the mammary fat. The failure to position correctly in these two cases may have been related to the indistinct and poorly defined margins of the invasive cancer as depicted at US. Real-time US monitoring was undertaken in all patients. After a delay of approximately 100 seconds, a gradually expanding hyperechoic (bright) region appeared around the fiber tip. The margin of the bright zone, however, was irregular and poorly defined. The hyperechoic area expanded to reach a peak 300–400 seconds into treatment and remained approximately the same size and shape until the end of therapy. At the cessation of treatment, the hyperechoic area gradually faded; 5 minutes after therapy the area was not discernible from the heterogeneous pattern of untreated tumor. In addition the changes seen at US were by no means consistent, and in two patients very little hyperechoic change was seen. The correlation was poor between the measured maximum hyperechoic zone during therapy and the histologic extent of laser-induced necrosis ($r^2 = .30$) (Fig 2a).

On the pretherapy MR images obtained in all cases, a foci enhancing mass depicted at FLASH imaging correlated with an invasive cancer in the surgical specimen. In three patients, areas of poorly defined, patchy enhancement were seen that corresponded histologically to DCIS. The presence of low-grade, homogeneous, diffuse but symmetric enhancement correlated with benign breast parenchymal changes and was considered a normal enhancement pattern. MR imaging depicted all the palpable tumors and five of the seven additional invasive tumors seen at histologic examination. In two patients the two missed cancers were additional invasive tumors that were each a 4-mm-diameter infiltrating ductal carcinoma. These tumors were obscured on the images by the presence of diffuse patchy enhancement around the main enhancing mass, which was interpreted as DCIS. MR images depicted DCIS in three of the patients with multifocal cancers. In the one patient with a unifocal invasive tumor and associated extensive DCIS, however, the MR image showed only a
unifocal enhancing mass of a size that correlated with the size of the combined in situ and invasive tumor. Prior to interstitial laser photocoagulation in two patients, the main enhancing mass exhibited a central area of nonenhancement that measured 10 and 8 mm in diameter and that corresponded to spontaneous tumor necrosis (Fig 3a) and mucinous matrix, respectively.

The median diameter of the enhancing masses was 21 mm (range, 8-40 mm). This correlated closely with the histologic size of the nine untreated and 13 treated tumors after interstitial laser photocoagulation (tumors in which the zone of laser-induced necrosis did not cross the tumor margin [median diameter, 20 mm; range, 4-33 mm]) \( r^2 = .90 \) (Fig 2b).

STIR and FLASH MR images obtained at 4 hours after laser therapy in the first three patients did not depict any change in the tumor. FLASH images obtained 24 hours after treatment, however, showed focal areas of nonenhancement within the enhancing mass in two patients. In the third patient, the fiber tip was incorrectly positioned in fat and no effect was seen. This experience changed our protocol for posttherapy imaging, and in subsequent patients images were obtained at a median interval of 48 hours after laser therapy (range, 24-96 hours).

In all gadolinium-enhanced images, the area of tumor necrosis was seen as a region of uniform nonenhancement with well-defined margins. Residual tumor was identified as a persistently enhancing region that surrounded the area of necrosis. The nonenhancing zone was centrally located within the invasive tumor in 13 patients (Fig 3) and was eccentric in five (Fig 4). In the two patients in whom the fiber was inadvertently positioned outside the tumor, no effect was visible on either the unenhanced or gadolinium-enhanced images. In one patient, ablation of the invasive tumor was nearly complete. Surgery was performed 10 days after interstitial laser photocoagulation, and microscopic examination of the resected specimen showed an area of elastosis, scarring, and necrosis 14 mm in diameter, consistent with laser therapy and subsequent healing. The only residual tumor was a thin incomplete rim (1 mm wide) of invasive cancer at one margin, in the only patient in whom any changes could be seen after interstitial laser photocoagulation on STIR or unenhanced FLASH images. The unenhanced FLASH image showed a 13-mm-diameter area of increased signal intensity with a central 3-mm-diameter dark spot (Fig 5a). The residual tumor, however, was seen on only the gadolinium-enhanced image (Fig 5b).

The region of nonenhancement on the gadolinium-enhanced MR images corresponded to the entire three zones of the histopathologically defined laser

Figure 4. Pretherapy transverse T1-weighted MR images of the right breast in a 35-year-old woman were obtained (a) before and (b) after contrast enhancement and show a 19-mm-diameter spiculated mass that enhances throughout (arrow). MR images obtained 72 hours after interstitial laser photocoagulation (c) before and (d) after contrast enhancement show a new eccentric area of nonenhancement that measures 12 mm in diameter (straight arrow), with a residual 8-mm-diameter enhancing residual tumor at the medial margin (curved arrow). (e) Microscopic specimen shows area of laser-induced necrosis (LN) that measures 13 mm in diameter, residual tumor (RT) that measures 10 mm in diameter, and the relationship of the tumor to the nipple (N). Arrows indicate the boundary between the laser-treated area and residual tumor. (Hematoxylin-eosin stain; original magnification, x2.)
burn in all cases. The median diameter of the laser-induced necrosis on the gadolinium-enhanced images was 10 mm (range, 7–18 mm) and at histologic analysis was also 10 mm (range, 5–15 mm). MR findings resulted in overestimation of the extent of laser necrosis in eight patients (median, 1.5 mm; range, 1–3 mm) and in underestimation of the diameter of the lesion by 1–2 mm in two patients. The correlation coefficients (MR vs histopathologic analysis) for diameters of the laser burn and the residual tumor were 0.80 and 0.86, respectively (Fig 2c, 2d).

**DISCUSSION**

Conservative surgery is a safe alternative to mastectomy in carefully selected patients with breast cancer. The characteristics of patients suitable for treatment with breast conservation have been summarized in the National Institute of Health Consensus report (12). The development of interstitial laser photocoagulation as a definitive minimally invasive therapy for breast cancer would necessitate that similar patient selection criteria be met. The clinical success of interstitial laser photocoagulation is thus dependent on an imaging technique that helps identify patients suitable for breast conservation and also depicts the extent of the therapy effect accurately. The laser therapy itself must not interfere with the assessment of prognostic criteria or with the choice of any other appropriate therapies, such as radiation therapy or chemotherapy.

The size of invasive tumors measured at MR imaging in our series correlated accurately with those measured at histologic analysis. With the exception of two small invasive tumors masked by intraductal carcinoma, all other invasive and in situ cancers in our series were accurately depicted at MR imaging. A number of recent reports illustrate the sensitivity of breast MR imaging for diagnosis of clinically and mammographically occult breast cancer and for depiction of the extent of local disease (9,10,13). The full extent of disease must be depicted prior to therapy to ensure additional multifocal disease is not missed. Findings at breast MR imaging may help select appropriate patients for treatment with breast conservation. The same criteria may also be used to help select patients for minimally invasive therapy with interstitial laser photocoagulation. Multifocal or multicentric disease and the presence of an extensive intraductal component may be a relative contraindication for interstitial laser photocoagulation.

In this study, we found that gadolinium-enhanced MR imaging performed 24–96 hours after interstitial laser photocoagulation accurately depicted the extent of laser-induced necrosis in almost all cases. Our experience is consistent with the observations made at delayed contrast-enhanced MR imaging after laser therapy in colorectal liver metastases (14) and, furthermore, lends histologic support to their presumption that nonenhancing areas indicate avascular necrosis and enhancing areas indicate residual tumor.

We found a close correlation between MR and histologic findings of the extent of laser-induced necrosis and residual tumor following interstitial laser photocoagulation. The greatest discrepancy between findings at MR imaging and pathologic examination was 3 mm, which may be partly explained by the inevitable small error that occurs when the lesions are measured and when the planes of imaging and sectioning are aligned. When residual tumor is depicted on posttherapy images, further therapy can be planned to complete tumor ablation. The results of this study confirm the importance of performing pretherapy MR imaging, as areas of nonenhancement may already exist in the untreated tumor. These areas (seen in two patients) were found to be a result of spontaneous tumor necrosis or mucinous matrix. Such a correlation has not been demonstrated in other breast MR series (10,15) but has been shown at MR imaging in experimental breast carcinomas (16). Comparison of pre- and posttherapy images allows detection of new areas of nonenhancement and of changes in tumor morphology. More importantly, findings at pretherapy imaging can help select patients who may be suitable for interstitial laser photocoagulation.

In one patient, we were able to achieve complete tumor ablation, with only a 1-mm-wide rim of invasive tumor left at one margin. When patients are treated surgically with wide local excision, the palpable lesion is resected, ideally with a margin of more than 10 mm of macroscopically normal surrounding breast tissue to ensure any microscopic disease is well clear of the resection margins. The attainment of tumor-free resection margins, initially or after reexcision, is the most important predictor of local control after breast-conserving treatment with lumpectomy and radiation therapy (17). Thus a similar approach of treating the mass plus a margin of normal tissue will be necessary to reduce the risk of leaving residual disease when treating patients with interstitial laser photocoagulation. If interstitial laser photocoagulation is ever used as a sole initial therapy, guided biopsy of the treated margins may be necessary to confirm disease clearance, which is analagous to biopsy of the tumor bed performed after surgery.

The histologic features in breast cancer after interstitial laser photocoagulation that we observed in this study were similar to those described by other authors in liver tumors after treatment (18,19). The cells in the...
photocoagulation will be limited to tumor localization and needle and that the role of US in interstitial laser photocoagulation is likely to permit accurate and fast imaging techniques, real-time monitoring of interstitial laser photocoagulation in breast cancer.

Other minimally invasive techniques currently under investigation in the treatment of breast tumors include radio-frequency heating and focused US. Results with these techniques have not been published yet, to our knowledge. Recently a focused US system for MR-guided tumor ablation has been described (30), but to our knowledge its results in breast tumor ablation have not yet been published.

With the introduction of heat-sensitive and fast imaging techniques, real-time monitoring of interstitial laser photocoagulation therapy may become possible (31). MR imaging is very sensitive to tissue-water mobility and distribution (32), and the temperature dependence of MR relaxation parameters such as T1 relaxation times and diffusion coefficients (33,34) make it particularly suitable for the demonstration and monitoring of thermal energy deposition in tissues (35). Dynamic MR imaging guidance of interstitial laser photocoagulation therapy in colorectal liver metastases with use of a T1-weighted temperature sequence has been demonstrated (36). Potentially, the use of real-time imaging to monitor laser effects in breast cancer will facilitate total tumor ablation at a single treatment. With the availability of open-access breast coils, it is now possible to place laser fibers through MR-compatible needles with MR guidance.
We are currently evaluating real-time MR monitoring of interstitial laser photocoagulation at our institution. The high degree of accuracy of breast MR in depicting the extent of necrosis and residual tumor as demonstrated in the present study helps validate findings at real-time MR imaging. Technically, however, there is a long way to go, and practical real-time monitoring will need to be performed on the new generation of MR imagers that have easier patient access.

These preliminary results indicate that it is technically feasible to produce laser-induced necrosis in breast tumors safely and to assess the extent of necrosis with contrast-enhanced MR imaging. Interstitial laser photocoagulation has the potential to become a one-day outpatient treatment for selected patients with breast cancer, without the routine need for general anesthesia. It offers the possibility of preserving the shape and size of the breast with minimal posttherapeutic morbidity. Further advantages may include its role in the treatment of small cancers in elderly patients who are not sufficiently fit to undergo surgery and in younger women with central tumors in whom mastectomy may be the only surgical option. Further research is necessary, however, to assess the efficacy and safety of such an approach and to develop open-access MR systems before interstitial laser photocoagulation can be compared with more conventional forms of minimally invasive therapy in controlled trials in patients with breast cancer.

Acknowledgment: We are grateful to the staff in the MR unit at the Middlesex Hospital, University College London Hospital Trust.

References

Staging of Symptomatic Primary Breast Cancer with MR Imaging

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OBJECTIVE. This study was designed to investigate the accuracy of contrast-enhanced MR imaging in the locoregional staging of symptomatic primary breast cancer and to determine the impact of contrast-enhanced MR imaging in planning surgical management.

MATERIALS AND METHODS. Ninety patients with primary breast cancer (including two bilateral cancers) diagnosed and treated on the basis of conventional triple assessment (clinical, cytologic, and mammographic examination) underwent MR imaging at 1.0 T using a three-dimensional fast low-angle shot T1-weighted pulse sequence before and after contrast enhancement. A short inversion time inversion recovery sequence was also obtained to evaluate the axilla of each patient. After resection, tumors were histopathologically mapped in detail and correlated with the extent of contrast enhancement on MR imaging.

RESULTS. On the basis of triple assessment, 53 cancers were treated by wide local excision, of which 17 (32%) had positive margins at excision. Residual disease at reexcision was detected in eight of these 17 patients, a finding that correlated accurately with the extent of contrast enhancement on MR imaging. MR imaging was more accurate than mammography in determining invasive tumor size (r^2 = .93 versus r^2 = .59), in depicting multifocality and extensive intraductal component (sensitivity, 81% versus 62%), and in assessing nipple–retroareolar complex. MR imaging–histopathologic correlation was possible in 75 axillae. Sensitivity and specificity for axillary node metastases were 90% and 82%, respectively.

CONCLUSION. MR imaging of the breast has value in the preoperative locoregional staging of symptomatic primary breast cancer and is useful in planning a single definitive surgical resection in patients with breast cancer.
(defined as those presenting with palpable breast masses, skin or nipple changes, or palpable axillary lymph nodes) may not be justified compared with the accuracy provided by combined clinical examination, mammographic with or without sonographic examination, and needle biopsy evaluation (triple examination) of breast lesions [10]. Needle biopsy can help provide histologic diagnosis with biochemical analysis for 25–60% of the cost of MR imaging [11]. The role of MR imaging in the local staging of suspected breast cancer has shown promising initial results [12, 13]. However, these results are based on relatively few patients, and these studies have not fully evaluated all of the parameters required in determining disease extent, including axillary node status.

This study was designed to determine the accuracy of MR imaging in the locoregional staging of symptomatic primary breast cancer diagnosed by triple examination and to identify clinical situations in which preoperative MR imaging may provide useful additional information in treatment planning.

Materials and Methods

Over a 2-year period, 90 patients with symptomatic breast cancers underwent MR imaging before surgical treatment. The median age of the study population was 49 years old (range, 29–80 years old). A preoperative diagnosis of breast cancer was obtained in all patients by means of fine-needle aspiration cytology or needle-core biopsy (n = 9) in equivocal cases. All patients were recruited from the breast clinics at University College London and the Royal Surrey County Hospitals, Guildford, United Kingdom. The study was approved by the ethics committees of both hospitals.

Of the 90 patients, 81 presented with a clinically palpable lump, including one patient with bilateral breast lumps. The clinical T stages at diagnosis included one patient with clinically palpable lump, including one patient with palpable axillary lymph nodes. Tumors were considered multifocal on mammography when two or more discrete suspicious masses were present. The presence of microcalcification separate from the mass or if seen in more than one quadrant was also considered suspicious for multifocal disease.

MR Imaging of the Breast: Technique and Interpretation

MR Imaging was obtained using a dedicated receive-only double breast coil on a 1-T scanner (Magneton 42 SP, Siemens, Erlangen, Germany). A transverse T1-weighted three-dimensional (3D) fast low-angle shot sequence (TR/TE, 187; flip angle, 40°; 128 × 256 matrix; 64 partitions; effective slice thickness, 2 mm; rectangular field of view, 410 mm; acquisition time, 4.57 min) was made before and after enhancement with gadolinium dimeglumine (Magnestat; Schering, Berlin, Germany) at a dose of 0.1 mmol/kg of body weight. The contrast material was injected rapidly via a presited IV cannula connected to a long line, thus avoiding the need to move the patient in between imaging studies. The enhanced 3D volume sequence was begun immediately after injection of contrast agent was completed. Only one sequence was made after administration of gadolinium. A short inversion time inversion recovery sequence (TI, 140 msec; TR/TE, 2660/30; flip angle, 140°; 160 × 252 matrix; effective slice thickness, 5 mm; slice gap, 50%) was made before contrast enhancement and fast low-angle shot sequence in all but eight patients. In all cases, MR imaging of the breast was performed within 1 week after the fine-needle aspiration cytology or core biopsy.

Mammographic Interpretation

All mammograms were assessed preoperatively by a radiologist experienced in X-ray mammography who had knowledge of the clinical findings only. Bilateral craniocaudal and oblique mammograms were performed preoperatively in all patients. Additional views were taken when necessary. The mammographic findings included a mass (n = 43), mass with associated microcalcifications (n = 10), mass with separate area of microcalcifications (n = 8), microcalcifications only (n = 16), asymmetric density (n = 3), and benign changes (n = 12).

The following features were recorded: number, site, and size (maximum diameter) of the suspicious masses; presence of microcalcifications (type, site, and extent); relationship to the nipple, pectoral major muscle, and the axillary region (for nodes). Tumors were considered multifocal on mammography when two or more discrete suspicious masses were present. The presence of microcalcification separate from the mass or if seen in more than one quadrant was also considered suspicious for multifocal disease.

Histopathologic Assessment

Fresh specimens were delivered to the laboratory. The orientation of the mastectomy specimen on the chest wall was obvious from the attached axillary tissue. In cases where WLE specimens were employed, the orientation was indicated by marking its margins with sutures. The specimens were sliced in the transverse plane relative to the patient at 5-mm intervals to correspond with the transverse MR images, pinned to a cork board, and fixed in 10% formalin solution. Specimens were examined for macroscopic disease and photographed to allow comparison with the transverse MR images. Tissue was taken from the quadrant that contained the primary tumor, nipple, and retroareolar regions. Further blocks were taken from tissue at least 2 cm from the gross outlines of the primary tumor, from the remaining quadrants, and from areas of interest indicated by review of MR images.
Disease extent was described as unifocal (single focus of tumor with defined borders of any size), multifocal (additional foci of infiltrating carcinoma in the same quadrant as the primary mass), or multicentric (additional foci of in situ or infiltrating carcinoma in quadrants other than that of the primary tumor).

The microscopic features including tumor size (maximum diameter), type, grade, presence of tumor necrosis, and associated ductal carcinoma in situ were recorded. EIC was defined as the combination of intraductal carcinoma comprising 25% or more of the area defined by the borders of the infiltrating tumor and intraductal carcinoma in adjacent tissue (either in sections free of the infiltrating tumor or extending beyond the infiltrating margins of the tumor). Also included in this group were tumors that were primarily DCIS with focal or multifocal invasion [14]. DCIS, if present as a separate focus from the invasive tumor, was measured and correlated with MR images.

Statistical Analysis

Linear regression analysis was used to compare the clinical, mammographic, and MR imaging size of tumors with histopathologic analysis.

Results

At MR imaging, the presence of a focally enhancing mass correlated with invasive carcinoma in all but two patients. In both patients, additional foci of enhancement suggesting multifocal disease were seen but not confirmed at histologic examination. The presence of diffuse or linear enhancement correlated with DCIS seen histologically in all but five patients. The latter included diffuse enhancement seen in the symptomatic breast in two patients and in the contralateral asymptomatic breast in three patients. False-positive diffuse enhancement correlated with sclerosing adenosis and atypical epithelial hyperplasia.

The median size of all primary invasive tumors (n = 85) on histologic examination was 21 mm (range, 6-60 mm), which correlated more accurately with MR imaging (median size, 24 mm; range, 6-60 mm; $r^2 = 0.93$) than did mammographic measurement (median size, 20 mm; range, 0-65 mm; $r^2 = 0.59$) (Figs. 1 and 2). The morphologic characteristics of the primary enhancing masses included spiculated edges or irregular borders (n = 70 [84%]) or well-defined borders (n = 15 [16%]). In these tumors, the distribution of enhancement was homogeneous (n = 55 [65%]), peripheral or rim pattern (n = 12 [14%]), or had patchy areas of nonenhancement within the main enhancing mass (n = 18 [21%]). The area of nonenhancement correlated with spontaneous tumor necrosis, area of tumor fibrosis, or mucinous change within the tumor.

The histologic type of cancers is summarized in Table 1. On the basis of triple assessment, 53 cancers were treated by WLE, of which 17 (32%) had positive margins at excision. Three unifocal invasive tumors, eight unifocal EIC-positive tumors, five multicentric tumors, and one patient with multicentric DCIS were included in the 17 with positive margins at excision. Residual disease at reexcision (12 further WLEs and five mastectomies) was detected in nine (53%) of these 17 patients.
in Table 2. MR imaging depicted all unifocal tumors, according to their mode of detection is shown in three unifocal cancers, invasive carcinoma was present at the resection margins of the WLE specimen. In all three cases, MR imaging showed a unifocal tumor whose size measured greater than the histologic size of the invasive tumor in the primary resected specimen. Further wider excision confirmed residual invasive disease in all three patients.

Of the 10 multifocal tumors, mammography was normal in two patients, unifocal in three, and concordant with histologic findings in the remaining five. MR imaging depicted the additional tumor foci in six patients only. Tumors missed by MR imaging included an additional invasive ductal carcinoma measuring 4 mm in diameter in two patients and separate foci of DCIS in two patients. In the former two patients, the index tumor had an adjacent EIC that was depicted on MR imaging as diffuse patchy enhancement adjacent to the focally enhancing invasive tumor and thus may have obscured the smaller invasive focus. In all 10 patients, primary surgical treatment based on clinical and mammographic measurement of index palpable tumor was definitive with adequate clearance. The median size of the additional clinically and mammographically occult invasive focus was 6 mm (range, 4–21 mm). Histologic examination in the patient treated by prophylactic mastectomies showed multifocal invasive lobular carcinoma in both breasts, including several foci of DCIS and lobular carcinoma in situ in the contralateral breast. MR imaging showed scattered areas of focal enhancement on the treated side and combined focal and diffuse enhancement in the contralateral untreated breast.

In four primary mastectomy specimens with multicentric invasive carcinoma, histologic examination also showed Paget's disease of the nipple, findings that were accurately depicted by MR imaging. A unifocal tumor in the remaining three. MR imaging depicted multicentric (in greater than one quadrant) invasive carcinoma in all five patients, and diffuse patchy enhancement was seen in all quadrants in two of these patients (Fig. 3). All five patients subsequently underwent mastectomy, and histologic examination confirmed multicentric invasive carcinoma, of which two were also EIC-positive.

In the 10 primary mastectomy specimens with multicentric cancer, MR imaging of the breast showed all multicentric invasive and invasive ductal carcinoma treated by prophylactic mastectomy, showed a unifocal tumor in two, and was concordant with histologic findings in the remaining six patients. The median size of the additional clinically and mammographically occult invasive focus was 6 mm (range, 4–21 mm). Histologic examination in the patient treated by prophylactic mastectomies showed multifocal invasive lobular carcinoma in both breasts, including several foci of DCIS and lobular carcinoma in situ in the contralateral breast. MR imaging showed scattered areas of focal enhancement on the treated side and combined focal and diffuse enhancement in the contralateral untreated breast.

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The histologic distribution of cancers according to their mode of detection is shown in Table 2. MR imaging depicted all unifocal tumors. In two patients, an additional enhancing mass was seen but did not correlate with invasive tumor at histologic examination. In three unifocal cancers, invasive carcinoma was present at the resection margins of the WLE specimen. In all three cases, MR imaging showed a unifocal tumor whose size measured greater than the histologic size of the invasive tumor in the primary resected specimen. Further wider excision confirmed residual invasive disease in all three patients.

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Fig. 4.—60-year-old woman with palpable breast lump and inverted nipple. A and B, Unenhanced (A) and enhanced (B) transverse T1-weighted MR images show enhancement of entire nipple and retroareolar tissue. Histologic examination confirmed Paget's disease of nipple with underlying invasive cancer.

Fig. 5.—32-year-old woman with history of blood-stained nipple discharge. A, Mammogram shows scattered microcalcifications (arrows). B and C, Unenhanced (B) and enhanced (C) transverse T1-weighted images show diffuse enhancement throughout breast cone. Enhancing breast tissue borders retrromammary fat (long arrow, C) and extends into retroareolar tissue (short arrow, C) with normal nipple. Histologic examination at mastectomy confirmed extensive comedo-type ductal carcinoma in situ (DCIS) with several areas of microinvasion. DCIS was present in lactiferous sinus but without nipple involvement. Tumor was within 1 mm of deep resection margin.

deighted on contrast-enhanced MR imaging (Fig. 4). Mammography confirmed nipple involvement in one patient, whereas clinical examination was suspicious for Paget's disease of the nipple in two patients only. In three mastectomy specimens, in situ carcinoma extended to the retroareolar zone with nipple sparing, findings that were seen on MR imaging as retroareolar enhancement with a normal non-enhancing nipple.

MR imaging depicted all seven cases of purely or predominantly DCIS as areas of diffuse patchy enhancement, the extent of which correlated with histologic examination (Fig. 5). Mammography showed microcalcifications in six patients but tended to underestimate disease extent in all cases (Fig. 5). Based on mammographic extent of microcalcifications, two patients underwent WLE, of whom one had positive margins at excision. Further wider resection based on MR imaging findings confirmed residual DCIS with adequate clearance. In one of the seven patients presenting with clinical evidence of Paget's disease of the nipple and treated by mastectomy, mammography showed increased density in the retroareolar region only. MR imaging in this patient showed multicentric diffuse patchy enhancement extending to and involving the nipple–retroareolar complex. Histologic examination showed multicentric comedo-type DCIS with no areas of microinvasion. Diffuse patchy enhancement suggestive of DCIS was also seen in one quadrant in three contralateral asymptomatic breasts, for which multiple needle-core biopsies showed benign proliferative changes only (Fig. 3).

In addition to the seven patients with purely or predominantly DCIS, an EIC was noted in 19 patients (11 unifocal, two multifocal, and six multicentric tumors). The extent of diffuse patchy enhancement adjacent to the focally enhancing mass correlated with the presence and extent of EIC in all but five breasts where the area covered by this form of enhancement correlated with sclerosing adenosis and atypical epithelial hyperplasia. The sensitivity and specificity of MR imaging for the presence of EIC were 81% and 93%, respectively. The sensitivity and specificity of mammographic microcalcifications (n = 34 mammograms with microcalcifications) for the presence of EIC were 62% and 74%, respectively (Table 3). Reexcision was done in eight unifocal EIC-positive tumors treated by WLE. Residual disease was not found in any patient.

The axillae of 78 of the 92 breast cancers could be assessed on MR imaging (Fig. 6), the remainder being obscured by cardiac flow artifact or not included in the field of view (n = 6) or inadequate MR imaging data (n = 8). MR imaging–histopathologic correlation was possible in 75 axillae (a further three axillae were excluded from analysis).
because of lack of histologic data). Poor correlation existed between the total number of malignant nodes seen on MR imaging and pathologic analysis. Using the outlined criteria, the sensitivity and specificity of MR imaging in the assessment of the presence of axillary node metastases were 90% and 82%, respectively, compared with clinical examination with a sensitivity of 53% (Table 4).

**Discussion**

The importance of the lumpectomy surgical margin status in long-term results of breast conservation has been emphasized in several studies [15, 16]. Studies of reexcision or mastectomy specimens after an initial biopsy have related the likelihood of residual carcinoma in the breast to the status of original margins [17, 18]. When tumor involved the resection margin, 50-67% of specimens were found to contain residual carcinoma. In the present series, nine (53%) of the 17 patients with positive margins at excision had residual carcinoma in the reexcision specimen. In all cases, the extent of residual carcinoma correlated closely with the extent of contrast enhancement on MR imaging. Thus, in the present series primary resection based on MR imaging measurement of tumor extent would potentially have improved the resection margin status in all cases with positive margins on excision. Also, the extent of reexcision (i.e., wider resection versus total mastectomy) was also accurately guided by MR imaging.

The presence of positive resection margins makes accurate pathologic measurement of tumor size difficult. An accurate preoperative estimation of tumor size is thus essential not only to guide the surgeon in the extent of primary resection required to achieve microscopically negative resection margins but also to provide an important independent prognostic marker [19]. In the present study, MR imaging measurement of invasive tumor size correlated more closely with histologic size than with mammographic measurements (correlation coefficient, .93 versus .59, respectively). These results agree with the greater reported accuracy of MR imaging compared with mammography for invasive tumor size measurement [5]. Flanagan et al. [20] showed that the size of a mass lesion on mammography had an almost 1:1 relationship with pathologic tumor size; however, such a lesion was found in only 27% of the patients with breast cancer seen in their practice over a 1-year period. In the symptomatic population, the presence of a palpable lump allows the surgeon to perform an adequate local excision in most cases. In this situation, the role of imaging is to confirm the absence or presence of multifocal disease and to define the extent of the intraductal disease associated with the index invasive tumor.

In the present series, the extent of residual disease in the mastectomy specimens of the six patients with clinically and mammographically occult multicentric carcinoma (five invasive and one pure DCIS) initially treated by WLE was accurately depicted on contrast-enhanced MR imaging. In contrast, all multifocal cancers (additional foci within the same quadrant as the primary) were adequately treated by the first resection based on clinical and mammographic measurements of the primary palpable tumor. These results suggest a role of preoperative MR imaging in patients who are selected for conservation therapy based on clinical and mammographic assessment alone.

However, in view of false-positive areas of contrast enhancement, caution needs to be exercised in changing treatment strategy in patients purely on the basis of multicentric cancers suspected on MR imaging. In the present series, false-positive contrast enhancement was seen in seven (7%) of the 95 breasts (two focally enhancing masses and five breasts with diffuse patchy enhancement). Because certain additional foci of enhancement depicted on MR imaging may be clini-
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cally and mammographically occult, an MR imaging–guided biopsy will be required to ascertain the nature of these lesions. Furthermore, the exact significance of discovering microscopic multicentric lesions on the basis of MR imaging alone remains undefined in the overall management, as currently all patients treated with breast conservation receive adjuvant radiotherapy. MR imaging would be of value in situations in which an otherwise occult invasive focus is shown that conventional radiotherapy cannot eradicate. When considering the design of future trials of radiotherapy versus no radiotherapy after breast conservation, MR imaging of the breast to exclude detectable multifocal or multicentric disease may warrant inclusion.

The sensitivity and MR imaging appearance of DCIS have been reported to be attributed to differences in MR imaging techniques and interpretative criteria. Using contrast-enhanced subtraction dynamic MR imaging, Gilles et al. [21] identified 34 of 36 patients with pure DCIS appearing as areas of nodular, ill-defined, or linear contrast enhancement. In the series of Orel et al. [13], MR imaging depicted four of six cases of pure DCIS with linear enhancement seen in only three cases; the MR imaging appearance in the fourth patient was not described. Of the two negative studies revealed by MR imaging in the latter series, diffuse enhancement of the breast tissue was seen in one patient with a 6.6-cm predominantly intraductal cancer but was interpreted as a normal variant of parenchymal enhancement. Nevertheless, other authors have considered diffuse enhancement (defined as ill-defined enhancement interspersed throughout the breast parenchyma) as abnormal. Using this criterion, Harms et al. [12] were able to depict all seven cases of DCIS in their series of 47 histologically proven cancers, whereas Kerslake et al. [22] identified seven of 13 cases of DCIS in which the DCIS extended beyond the margins of the invasive tumor. In our series of seven patients with pure DCIS, contrast enhancement was seen as areas of diffuse enhancement that correlated accurately in their extent with histologic analysis. Mammographic microcalcifications were seen in six patients but tended to underestimate the extent of DCIS seen histologically.

In addition, in the present series 47% of invasive tumors had an associated intraductal component that is a characteristic feature of primary breast carcinoma. In a study of 20 quadrantectomy specimens, Ohtake et al. [23] showed intraductal extension in 80% of cases that was continuous from the primary invasive carcinoma through the mammary duct tree. The imaging correlates of this pathologic finding have not been discussed fully in previous studies. In tumors with minimal DCIS confined to their margin, MR images in our series showed a focally enhancing mass with size that correlated with the combined histologic size of the invasive and intraductal cancer.

In EIC-positive invasive tumors, MR imaging showed an adjacent area of diffuse or linear enhancement in addition to the focally enhancing mass. The extent of diffuse enhancement around the focally enhancing mass correlated closely with both the presence (sensitivity, 76%; specificity, 92%) and the extent of EIC compared with mammographic microcalcifications (sensitivity, 52%; specificity, 88%). In the five false-negative cases (in whom mammographic microcalcifications were also not seen), MR imaging showed only a focally enhancing mass. False-positive diffuse enhancement was seen in five patients for whom the histology showed atypical epithelial hyperplasia and sclerosing adenosis. Of the benign breast lesions, sclerosing adenosis has been shown to enhance consistently with gadolinium [11]. Previous MR imaging studies have not fully evaluated its role in the depiction of EIC-positive tumors. Boetes et al. [5], in a subset of eight patients, showed that MR imaging underestimated the extent of EIC by 1 cm in all cases but did not describe the MR imaging appearance that differentiates DCIS from invasive tumor. Our results suggest that the presence of diffuse enhancement on MR imaging of the breast should be further evaluated by MR imaging–guided needle biopsy so that a single definitive surgical procedure (i.e., a wider resection or mastectomy) can be performed in this group of patients.

Recognition of nipple involvement with tumor preoperatively is of critical importance in selecting patients who may be unsuitable for breast preservation surgery or nipple preservation mastectomy. The mammographic changes associated with Paget’s disease of the nipple are nonspecific with more than 50% of patients with clinically evident disease reported as having normal mammograms [24]. The preliminary observation in our study suggests that MR imaging is more sensitive than mammography and clinical examination in the evaluation of the nipple–retroareolar complex.

To our knowledge, the MR imaging features of Paget’s disease of the nipple have not been fully evaluated. Harms et al. [12], in a retrospective analysis, noted nipple involvement in two MR images previously interpreted as being the normal enhancement pattern of the nipple–retroareolar complex. Using dynamic MR imaging, Kaiser [25] showed a rapid initial enhancement of the nipple that exceeded 100% of the unenhanced signal intensity during the first minute after injection of contrast material in Paget’s disease of the nipple. This criterion allowed an accurate diagnosis in four patients, in all of whom nipple involvement was missed on mammography. These preliminary observations suggest that MR imaging may have a role in the assessment of the nipple–retroareolar complex. This information may enable safe preservation of the nipple in patients with centrally placed breast tumors, allowing for more cosmetically acceptable results associated with nipple-preserving mastectomy.

The accuracy of MR imaging in revealing axillary node metastases has not been previously reported, to our knowledge. In a subgroup of patients in this series, using specific criteria, we found MR imaging to have a sensitivity of 90% and a specificity of 82% in the diagnosis of involved axillary nodes. The criteria used in the diagnosis of metastatic nodes in our series may be applicable only in the symptomatic breast cancer patient. Further experience in screen-detected cancers needs to be acquired, and different criteria may need to be adopted. The present limitations of axillary MR examination are largely caused by the breast coil design, which does not optimally cover this region, and the associated cardiac flow artifact projected over the axilla during MR imaging of the breast. Although the latter limitation can be minimized by scanning the breast with the phase and frequency switched in the appropriate direction, the use of radiofrequency coils specifically designed for axillary imaging will improve the overall accuracy of MR imaging in determining the extent of axillary node disease.

In conclusion, this study has shown that preoperative MR imaging of the breast can provide additional information with clinical benefits in guiding treatment selection for patients with breast cancer diagnosed on the basis of conventional triple assessment. This information can be useful in planning surgical management, thus reducing the need for repeated excision and patient anxiety.
References