INTERSTITIAL LASER PHOTOCOAGULATION AS A TREATMENT FOR BREAST CANCER

Thesis submitted for the degree of

Master of Surgery

in the

University of London

by

Simon Anthony Harries

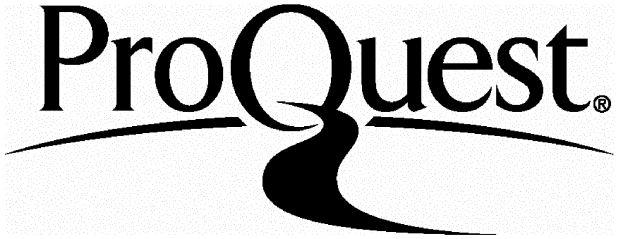
M.B. B.S., F.R.C.S.(Eng.)

The National Medical Laser Centre,

Department of Surgery, University College London Medical School,

London.

June 1994



Abstract

Conservative surgery is a safe alternative to mastectomy for some patients with breast cancer. A survey of surgeons in this thesis has shown that more surgeons would now undertake conservative surgery than they have done in the past. Recently a new technique, interstitial laser photocoagulation(ILP) has been described which is capable of *in situ* tissue necrosis with safe healing. The idea of ILP takes the concept of conservative surgery for breast cancer a step further. The main purpose of this thesis was to investigate the potential value of ILP as a future method of destroying breast cancers *in situ* leaving the area to heal via resorption and fibrosis.

The aims of this thesis were to study the biology of laser interactions with breast cancers scheduled for surgery(and not to completely destroy the tumour), to optimise the laser parameters of power and exposure for a particular tumour and to find an imaging technique which will accurately predict the extent of laser damage. Forty five patients were treated with ILP prior to surgery(median 7 days). Tumour necrosis varied from 2-25mm. No laser damage was noted in 4 patients. Two patients developed minor complications and treatment was abandoned early due to pain in a further 4 patients. The presence of charring within the tumour was associated with larger diameters of necrosis than when charring was absent(median 13 vs 6 mm, p=0.002) and use of a pre-charred fibre produced similar lesions(median 14mm) which were more predictable.The histological features in the tumour following ILP were of coagulative necrosis which appeared to heal by the formation of fibrous tissue. An area of heat fixed, morphologically preserved tissue was noted within the zone of coagulative necrosis which was thought to be non-viable.

Ultrasonography, Computerised Tomography(CT) and Magnetic Resonace Imaging(MRI) were all used to monitor necrosis. Ultrasound was unable to predict the extent of necrosis as measured in the resected specimen(r=0.3, p=N.S.) but was reasonable at predicting tumour size(r=0.6, p=0.001). CT and MRI show some promise but were only investigated in small numbers of patients.

This study has shown that ILP is simple and safe and when using a pre-charred fibre, predictable. If the initial results of imaging using CT and MRI are confirmed in larger studies then ILP could possibly have a role in the treatment of small breast cancers.

Contents

List of tables and illustrations

Tables

Chapter 2

Chapter 5

Chapter 6

Chapter 8

Illustrations

Chapter 4

Chapter 6

a)skin b) position of the fibre tip c) area of necrosis d) viable tumour e) charring.

Chapter 7

Figure 7.1: The cavity(A) with evidence of charring lining the cavity(arrowed),the area of *in situ* fixation(B) and surrounding necrosis(C) seen in a tumour excised 12 days after ILP using a clean fibre at 2 watts for 500 seconds.

Figure 7.2: The area of *in situ* fixation in greater detail(same specimen as figure 7.1) showing elongation of the nuclei and spindle like cells in a patient with a pure ductal carcinoma in situ.

Figure 7.3: In areas, the zone of *in situ* fixation(same specimen as figure 7.1) did not differ in appearence from viable tumour tissue. This figure shows an area of ductal carcinoma in situ within zone B.

Figure 7.4: The junction between the *in situ* fixation and necrotic tissue 12 days post ILP, there is no evidence of inflammation.

Figure 7.5: The zone of necrosis(zone C) showing a) pyknotic cells b) haemorrhage c) ghost like cells after karyolysis 3 days after ILP using a clean fibre 2.5 watts for 500 seconds.

Figure 7.6: Thrombosis evident 3 days after ILP in the outer aspect of zone C(arrowed). The laser was activated at 2.5 watts for 500 seconds using a clean fibre.

Figure 7.7: Acute inflammatory response(polymorph arrowed) at the interface between necrotic tumour(zone C) and normal tissue 3 days after ILP using a clean fibre, 2.5 watts for 500 seconds.

Figure7.8: Junction between zone C and normal breast tissue 7 days after ILP(fibroblasts arrowed)

Chapter 8

area marked by the black ink) which was not visible on ultrasound.

Figure 8.5: CT scan 24 hours after ILP. The tumour enhances (a) showing a devascularised area (b) which measures 15mm. The final diameter of necrosis measured 11mm histologically when resected 12 days after ILP.

Figure 8.6: CT scans seen 24 hours post ILP. 8.6a) post laser pre-contrast 1=fibre tract 2= tumour and 8.6b) post laser post contrast 1=fibre tract 2=tumour 3=laser induced necrosis.

Figure 8.7: CT scans seen in real time, no demonstrable changes were visible.a) pre laser post contrast(tumour arrowed) b)during ILP treatment needle(1) and tumour(2). Following treatment no changes were visible either in the tumour or surrounding tissue on CT scanning but 8mm of laser damage was subsequently found in pectoralis major.

Figure 8.8: MRI scans 24 hours post ILP(patient 3), a) pre-laser pre-contrast, the tumour is arrowed, b) post laser pre-contrast(laser fibre track arrowed) and c) Post laser post contrast an area of reduced enhancement is evident(arrowed) which corresponded exactly with the histology(d).

Figure 8.9: MRI scans a) pre laser pre-contrast b) pre-laser post contrast, the tumour enhances(arrowed) c) post laser pre-contrast and d) post laser post contrast

Acknowledgements

The work included in this thesis was undertaken at the National Medical Laser Centre, in the Department of Surgery at University College London Medical School and in the Department of Surgery at The Royal Surrey County Hospital, Guildford, Surrey. I am particularly grateful to my supervisors, a special thanks goes to Professor Steve Bown, who thought of the concept of ILP and initiated this project, for his continued support, abounding enthusiasm and encouragement and to Mr. Mark Kissin for his support, enthusiasm and ideas. Mark taught me a lot about breast disease in the breast clinic at Guildford and fired my enthusiasm to pursue a general surgical career with a strong interest in breast disease. To you both I am very grateful.

The work contained in this thesis and my salary were provided by the Guildford Laser Appeal and I am particularly indebted to Mrs. Gillie Ross chairwoman and the Ladies and gentleman of the appeal committee for all their extremely hard work in raising the money to support me. I would especially like to thank the kind ladies of Guildford and London who agreed to take part in the study armed with the knowledge that the technique would have no direct benefit for them but possibly for women like them in the future. It was at the suggestion of Mr.R.C.G.Russell that I was introduced to Professor Bown and the ILP project and I am grateful for his guidance and advice during the last 2 years and to another of my old mentors, Mr.John Scurr who also assissted me financially. Professor Irving Taylor and Mr.Tim Davidson have scrutinised some of the chapters contained herein and I am grateful for their help and suggestions. Dr.Tim Mills, Dr.Giovanni Buonaccorsi and Dr.Matthew Clemence from the medical physics department have been of invaluable assistance non the least in teaching me some physics! Dr.Bill Lees and Dr. Julie Cooke, both consultant radiologists were of great help and taught me how to perform breast ultrasound. I am grateful to pathologists Dr.Martin Cook and especially to Dr.Mark Smith for their help and enthusiasm in the project. I would also like to thank Dr Waddy Gedrojk, consultant radiologist in the MRI unit at St. Mary's Hospital, London and G.E.medical systems, Millwaukee who funded Dr.Clemence and the breast MRI's which were performed in

their breast MRI coil at St.Mary's Hospital. Thank you also to Dr.Tony Raven, Mr.Ilka Mannonen and Mr.Ian Cameron from Diomed Ltd., Cambridge for loan of the laser and for all their invaluable assistance. Sisters Pat Willgoose and Dorothy George, breast care nurses at Guildford and London, Pat Jenkins sister in the Jarvis Breast Screening Centre and Sister Ann Aldborough, endoscopy sister at University College Hospital were all of enormous help. I am also grateful to Mr. Abdul Gafur and the staff of the medical illustration department at the Middlesex Hospital for excellent photographic assistance. A special thanks goes to Mr. Ross Scrivener, facilitator in the medical audit department for creating the database and loading data onto the computer for chapter 5. I am indebted to Dr.Secker Walker and Dr Jane Silk from the medical audit department and Farmitalia Carlo Erba Ltd. for funding the questionnaires(chapter 5). I am also grateful to Dr. John Bulmer of the Eastman Dental Hospital for statistical advice. Miss Amanda J.S. Jones, secretary to Professor Bown has been of enormous help especially with the computers. I am grateful to those I have shared an office with over the last 2 years who have been most supportive and friendly, Dr. Glen Spencer, Miss Sally Thorpe, Dr. Zahir Amin, Dr. Hugh Roberts, Mr. Isaac Nyamecke, Dr Charles Millson, Dr. Ian Sergeant, Mr.Ken Anson and Mr. Kenneth Port.

And finally a special thanks to my wife Tamara for all her help and support and tolerance over the last two years. Without you all, I would not have written this thesis.

Dedication

To my wife Tamara

and to my parents

Marion and Derek

CHAPTER 1: BREAST CANCER : METHODS USED TO OBTAIN THE DIAGNOSIS

1.1 Tissue diagnosis

1.1.1 Introduction

1.1.2 Fine needle aspiration cytology(FNAC)

1.1.3 Core biopsy

1.1.4 Excision biopsy

1.2 The imaging of breast cancer

1.2.1 Mammography

1.2.2 Ultrasound

1.2.3 Colour doppler ultrasound

1.2.4 Computerised Tomography(CT)

1.2.5 Magnetic Resonance Imaging(MRI)

1.2.6 Other techniques

1.2.7 Summary

1.1 Tissue diagnosis

1.1.1 Introduction

The modern management of a patient with breast cancer requires that a certain amount of tissue be obtained from the tumour not only to confirm the diagnosis of malignancy but also to give an indication of tumour type and grade in order that appropriate adjuvant treatment can be planned. For instance, the treatment of a patient with a pure ductal carcinoma in situ will be different from that of a patient with an aggressive grade III ductal carcinoma and different again from a patient with a tubular carcinoma. The main methods available to obtain tissue from a patient with a suspected breast carcinoma are fine needle aspiration cytology, core biopsy and excision biopsy.

1.1.2 Fine needle aspiration cytology(FNAC)

Fine needle aspiration cytology(FNAC) was initially introduced by Martin and Ellis in 1930 and is a reasonably simple technique(often deceptively so!) which requires little in the way of equipment but a fair degree of skill in order to obtain sufficient material and considerable skill in interpretation requiring an experienced cytologist. The use of FNAC as a method of obtaining a tissue diagnosis has accelerated in popularity in the past 10 years or so and some centres now have a cytologist in the clinic who not only performs the FNAC's but also reports the results immediately. Basnett et al(1992) showed how the use of breast FNAC increased in the period 1982-86 in a teaching and a non-teaching hospital. The technique obviously depends upon there being sufficient material in the aspirate to make a diagnosis and in the larger series(Ciatto et al, 1993a) the inadequacy rate was 6.9% for cancers and 24.1% for benign lesions. Cytology can give a definitive diagnosis of malignancy, can give an indication of tumour type and in some cases an indication of tumour grade(Hunt et al, 1990, Ciatto,1993b), oestrogen and progesterone receptor status(Weintraub et al, 1987, Redard et al, 1989) and even proliferative indices(Remvikos et al, 1991). FNAC does have its limitations, for example, it cannot distinguish malignant cells from an in situ carcinoma from malignant cells from an invasive carcinoma with any degree of accuracy and it is certainly not possible at the present time to plan subsequent therapy for early breast cancer(apart

from surgery) just on the results of a positive FNAC. Fentiman(1990) has recently published an overview of 10 studies evaluating FNAC and subsequent histology. The number of patients in these studies ranged from 369 to 3545. The sensitivity of FNAC was on average 87% and the specificity 99% with a positive predictive value of 97%. A large single centre study published recently by Ciatto et al(1993a) analysed 9533 cases of breast FNAC. The overall sensitivity was 89.5% and was dependent upon histological type with a sensitivity of 90.1% for invasive ductal carcinomas, 79.6% for in situ ductal cancers, 84.5% for invasive lobular carcinomas and 90.6% for special type cancers. The specificity in this series was 98.5%. Therefore, FNAC is a reliable, safe and simple technique but does require some skill in the performance of the technique and interpretation of the specimens and the information gained is limited.

1.1.3 Core biopsy

The technique of core biopsy involves the insertion of a larger bore needle into the tumour consequently producing more tissue from which to make a definitive diagnosis. Usually the Trucut® or Bioptycut® devices can easily be used under local anaesthesia in the outpatient clinic. Fentiman(1990) has reviewed 7 studies evaluating the value of Trucut® needle biopsies for the confirmation of malignancy in breast masses. The 7 series included between 87 and 278 breast cancers, the average sensitivity from the 7 series was 82% with a specificity of 100% and a positive predictive value of 100%. Trucut® biopsies can give much more information about tissue type and can differentiate between invasive and in-situ cancer, although the results have to be interpreted with caution(the presence of in-situ disease in a biopsy does not exclude invasive disease elsewhere in the lesion). Core biopsy can also give an indication of tumour grade, steroid hormone receptors and tumour type. Baildam et al(1989) studied 140 patients who had trucut biopsies and subsequently underwent surgery in order to ascertain exactly how much information can be obtained from core biopsies by comparison with the final resected histological specimen. One hundred and thirty had carcinomas. The sensitivity was 95% and the specificity 100%. In 93% of cases the pathologist was able to type the tumour correctly and in 69% was able to correctly

grade the tumour but lymphatic invasion or elastosis could not be accurately predicted. In 28% of cases it was possible to perform DNA flow cytology and in 45% of cases steroid receptor assays. This study confirmed that core biopsies were capable of providing a reasonable amount of information prior to surgery.

1.1.4 Excision biopsy

With the advent of FNAC and the use of core biopsies the use of excision biopsy as a means of obtaining a tissue diagnosis has declined. Sometimes it is necessary to perform an excision biopsy in the face of a patient with a persistent breast lump when FNAC and core biopsies were normal and it is still necessary often for patients with screen detected abnormalities. The use of excision biopsy as a primary method of obtaining a diagnosis has now largely fallen into the archives of surgical history although it is still practiced in some centres(see chapter 5). The practice of excision biopsy results in many patients undergoing unnecessary surgery and in some cases more than one surgical procedure.

1.2 The imaging of breast cancer

1.2.1 Mammography

The technique of mammography was first reported by Warren in 1930 and popularised by Egan in 1960 who reported a series of 1000 cases with a sensitivity of 97%. Mammography is an excellent technique for the detection of lesions within the breast but it is fairly non-specific; the classical radiological signs suggestive of malignancy being a spiculated mass with ill defined margins, the presence of architectural distortion or skin thickening and characteristic fine microcalcifications. Mammography can confirm the presence of malignancy diagnosed clinically and is essential for any woman who presents with breast cancer, firstly to exclude multicentricity and multifocality and secondly to exclude impalpable contralateral breast cancer(Dixon and Chetty, 1991). Mammography can detect early impalpable cancer and can predict the presence of an extensive intraduct carcinoma within an invasive carcinoma(Dixon and Chetty, 1991, Stomper and Connolly, 1991), a known risk factor predicting local recurrence following conservative breast cancer surgery . The sensitivity of mammography depends upon many features probably the most important of which is patient age. The pre-menopausal dense breast is more difficult to visualise on mammography than the older, post menopausal fatty breast and this is reflected in the sensitivity of the technique for malignancy. The overall sensitivity of mammography is between 61-87%(Fentiman, 1990) with an average sensitivity of 70% obtained from 10 series(Fentiman, 1990) but for women under 50 years the figure was 56% compared to 78% for those over 51 years. Mammography is said to be less accurate at diagnosing infiltrative lobular carcinoma(Fentiman, 1990) possibly because lobular carcinoma produces masses which are of relatively low radiologic opacity similar to normal fibro-glandular breast tissue and in addition lobular carcinomas tend, as reported in some series, to have less in the way of worrisome microcalcifications when compared to invasive ductal carcinomas(Krecke and Gisviold, 1993). Mammography is not an accurate tool for measuring tumour size(Pain et al, 1992) tending to underestimate the size of larger tumours and in this study it was not possible to determine the size of some of the

tumours(in 18% of cases). Another series(Report from the Yorkshire Breast Cancer Group, 1980) found concordance between radiological(by mammography) and pathological tumour size in 59% of 348 cancers and Fornage et al(1987) found a correlation coefficient of 0.72 between mammographic and pathologic tumour size in a study of 31 patients.

1.2.2 Ultrasound

Ultrasound is now well established as an indispensable complementary investigation to mammography in the diagnosis of breast disease. Ultrasound is not useful as a screening modality being unable to detect fine microcalcifications(Muir et al, 1983, Sickles et al, 1983) but is extremely useful in differentiating an impalpable cystic from an impalpable solid lesion seen on mammography with reported accuracy's in the range of 96-100%(Greenstein Orel and Troupin, 1993). Ultrasound can also be useful in differentiating solid from cystic palpable lesions which are not seen on mammography due to a dense fibro-glandular background and can be used to guide interventional procedures such as fine needle aspiration cytology(for example of an impalpable solid lesion detected on mammography). Ultrasound is unable to differentiate solid lesions which are benign from solid malignant lesions although both benign lesions such as fibroadenomas and carcinomas are said to have characteristic echoic appearances. The sensitivity of ultrasound varies in reported series from 68-93% with an average of 84%, a specificity of 89% and a positive predictive value of 88%(Fentiman, 1990). Pain et al(1992) found that ultrasound consistently underestimated tumour size as measured by subsequent histology reporting a correlation coefficient of 0.75 and a correlation coefficient of 0.84 was found in a similar study by Fornage et al(1987) with ultrasound tending to overestimate tumour size.

1.2.3 Colour doppler ultrasound

Malignant breast tumours stimulate the growth of new blood vessels by the release of angiogenesis factor giving rise to characteristic features on colour doppler sonography. Cosgrove et al(1993) recently reported the use of colour doppler ultrasound in 210

patients with 222 breast lesions including 58 breast cancers. Colour doppler signals were obtained from 57 of the 58 breast cancers with an average of 2.16 vessels per lesion compared to colour doppler signals from 5 of 104 patients with benign breast changes and 5 out of 36 patients with fibroadenomas and 7 out of 12 patients with miscellaneous conditions(which included 4 cases of breast infection all of which gave colour doppler signals). Cosgrove et al(1993) described a sensitivity of 98% and a specificity of 89%. The technique has not been reported to be so accurate by other workers, McNicholas et al(1993) reported a sensitivity of 87% with a specificity of 32% in a study of 54 cancers and 77 benign lesions and cite an overall sensitivity of 87%, a specificity of 70% and a positive predictive value of 82 % from 4 series reported in the literature.

1.2.4 Computerised Tomography(CT)

CT scanning of the breast has not been shown to be of value in the routine detection of breast cancers. The early enthusiasm for the technique in the late 1970's and early 1980's was based on the work of Chang et al who found that carcinomas enhanced with the use of iodonated contrast but other workers have found that reliable differentiation between benign and malignant tumours could not be achieved despite the administration of intravenous contrast(Greenstein Oriel and Troupin, 1993). In addition the use of CT results in a higher dose of radiation than mammography both to the breast and to the thorax and the technique is considerably time consuming and relatively expensive. Hence breast CT has not found a place in the routine imaging of breast cancer.

1.2.5 Magnetic Resonance Imaging(MRI)

Magnetic Resonance Imaging allows visualisation of the breast without radiation, in fact, some of the earliest clinical work done on MRI was on the breast. The principle of MRI is based on the fact that some nuclei(with unpaired electrons) behave like small magnets. Water is the principle constituent of most body tissues and the hydrogen nuclei are therefore present in large numbers. The use of a strong external magnet will force the nuclei to align in a new magnetic axis, a pulse of radiowaves then displaces

the magnetised nuclei from their new alignment releasing the energy they absorbed as a radiosignal and this signal is detected by the coil used for excitation. The signal is then converted by computer into an image. The magnetic fields used in clinical practice range from 0.15 to 1.5 Tesla(or 1500 to 15000 Gauss where the earth's magnetic field is 0.5 Gauss). The main radiofrequency pulse sequences used are called saturation recovery, inversion recovery and spin echo. Inversion recovery sequences(T1 weighted images) show better anatomical detail whilst spin echo(T2 weighted images) sequences are better at imaging pathological changes. MRI has good soft tissue resolution and has been investigated by several workers as a potential imaging device for the breast.

The early reports of the use of breast MRI were encouraging(Greenstein Orel and Troupin, 1993) but large slice thickness with long acquisition times and initially only moderate sensitivities diminished the initial enthusiasm for breast MRI and its future place in the diagnosis of breast cancer was uncertain. However, more recent developments including the use of breast surface coils instead of body coils, improved signal to noise ratios, the use of intravenous gadolinium to enhance the tumour and fat suppression sequences have all significantly increased the sensitivity of breast MRI and another surge of enthusiasm has resulted. For MRI to have a major role in breast cancer diagnostic management it must, a) have high resolution for detection of small cancers (this requires intravenous gadolinium to enhance the tumour to increase the sensitivity), b) employ fat suppression sequences for differentiating enhanced tumours from breast fat and c) have rapid acquisition times(less than 6 minutes) for differentiation of enhancing tumours from breast parenchyma(Harms et al, 1993). MRI has much higher sensitivities for malignancy than mammography, Kaiser(1993) reported a 98.4% sensitivity for detection of 63 carcinomas and Harms et al(1993) a 94% sensitivity for the detection of 47 carcinomas. Harms et al(1993) also found a good correlation between tumour size as measured by MR and subsequent histology. It appears that intravenous administration of the paramagnetic agent gadolinium increases sensitivity. In one study 20% of cancers were observed only after administration of gadolinium(Kaiser and Zeitler, 1989) and in this series 8 cancers were visualised on

MRI which were not seen on mammography. When tumours do enhance they sometimes appear isointense with the surrounding breast fat but fat suppression sequences have now been developed to overcome this problem(Pierce et al, 1991). The third problem is that enhancement of breast cancers with gadolinium is due to the difference in vasculature between tumour tissue and normal breast tissue, essentially benign lesions such as fibroadenomas can enhance and in time the surrounding normal tissue will enhance as well. Hence the need for rapid acquisition sequences as benign tissue enhances much more slowly than tumour tissue. The fact that benign lesions and in time breast parenchyma will enhance with gadolinium results in breast MRI having a high false positive rate varying from 18-40%(Hussman et al, 1993).

As well as in primary diagnosis MRI probably has a place in the detection of local recurrence in the breast(Lewis-Jones et al,1991)following breast conserving surgery and radiotherapy where it may be difficult on mammography, especially in the premenopausal dense breast, to differentiate between local recurrence and post operative scar tissue, as scar tissue does not enhance with gadolinium, although 1 report suggested that scar tissue will enhance in the first 6 months after surgery(Cohen, 1993). It may also be possible in the near future to perform stereotactic needle localisation under MRI control or even minimally invasive procedures following the recent description by Hussman et al(1993) of early work with a MRI stereotactic localisation device for the breast.

MRI then has potential as a future imaging device for breast disease, it has greater sensitivity than mammography if gadolinium is given to enhance the tumour but has a lower specificity and in addition it is more time consuming, more expensive and less readily available than mammography. Current work in progress suggests that a stereotactic device could soon be available to allow biopsy or interventional procedures under MRI control but the future role of breast MRI has yet to be fully determined.

1.2.6 Other techniques

A variety of other techniques have either been investigated and abandoned or are currently under investigation seeking to find a role to play in diagnostic breast radiology. Thermography comes under the auspices of the first category(i.e.it has largely been abandoned). Greenstein Orel and Troupin(1993) reviewed the published results of thermography and found that it was associated with an unacceptably high false negative rate(49.5% of cancers were missed in one study!) and there is no current data to support its use. Similarly they reviewed the place of transillumination, a light scanning technique again associated with a high false negative rate(transillumination only detected 19% of tumours less than 1cm compared to mammography which detected 90% in 1 series).

Whilst these techniques are not in current use digital mammography is a new technique which has been described as "the evolving technology with the greatest potential impact on breast cancer detection and diagnosis"(Greenstein Orel and Troupin, 1993). Digital mammography is thought to have great potential in detection of lesions in the mammographically dense breast an area where mammography has only moderate sensitivity. However, it is still at an early stage of development and clinical evaluation. Another technique, Positron emission tomography(PET) scanning has been evaluated and is able to detect breast cancers with the aid of FDG(2-[F-18]-Fluro-2-deoxy-D-glucose) and F-18-ES (16-[F-18]-fluroestradiol-17). PET scanning may be able to monitor changes in the primary tumour following primary chemotherapy(Greenstein Orel and Troupin, 1993) and it appears that PET with F18ES may be able to predict the oestrogen receptor status of a tumour(Mintum et al, 1988). PET is at a very early stage of development in breast disease and has yet to find a role.

Summary

It is important to assess the patient with a suspected breast cancer thoroughly in order to plan subsequent treatment appropriately. A tissue diagnosis of malignancy can be reliably achieved by the use of fine needle aspiration cytology(FNAC) which has

largely replaced excision biopsy for this task, the information gained from FNAC is limited and more information can be achieved by means of a core biopsy.

Mammography is currently the standard imaging technique for the breast and is essential for all women who present with breast cancer. It has good sensitivity for the detection of malignancy but the sensitivity is lower in younger women. Ultrasound is a useful adjunct to mammography, its main value being to differentiate between a solid and cystic lesion. Colour doppler is currently under evaluation as is digital mammography. MRI shows great potential as an imaging tool for the breast but its exact role has yet to be defined. Breast CT, thermography and transillumination are now largely obsolete and PET scanning is at a very early stage of development.

CHAPTER 2 : THE TREATMENT OF LOCALISED BREAST CANCER

2.1 Surgery

2.1.1 History : The latter part of the Nineteenth Century onwards.

2.1.2 Trials comparing mastectomy and breast conservation.

2.1.3 Breast conservation.

2.1.3a Introduction

2.1.3b Cosmesis and patient acceptability

2.1.3c Local recurrence

2.1.4 The treatment of the axilla

2.2. Radiotherapy

2.3 Chemo-endocrine therapy

2.1 Surgery

2.1.1 History : The latter part of the Nineteenth Century onwards

Towards the latter part of the nineteenth century the standard treatment for breast cancer was mainly by local excision. The published results of this form of treatment revealed unacceptably high local recurrence rates (see Table 2.1)

Author	time period	no.cases	local recurrence rate
Bergmann	1882-1887	114	51-60%
Billroth	1867-1876	170	82%
Czerny	1877-1886	102	62%
Fischer	1871-1878	147	75%
Konig	1875-1885	152	58-62%
Kuster	1871-1885	228	60%
Von-Volkman	1874-1878	131	60%

Table 2.1 : Local recurrence rates following wide excision for breast cancer.
(from Harris, Hellman, Henderson and Kinne, 1991)

Charles Hewitt Moore(1821-1870) a surgeon at St. Luke's and the Middlesex Hospital in 1867 was one of the first surgeons to encourage more extensive surgery for breast cancer. Believing that local recurrences were due to a continuation of the growth of fragments of the primary tumour, he advised excision of the primary tumour along with any tissues likely to be affected- including skin, fat, muscle and lymphatic tissue. His ideas laid the foundation for the development of more radical surgical procedures which were to revolutionise the treatment of the disease at the end of the nineteenth and for much of the twentieth century.

William Stewart Halsted in 1894 reported his results with the operation of radical mastectomy which he first performed in 1882 and described a local recurrence rate of only 6% in the 50 patients that he operated on(Halsted, 1894). These results were in

stark contrast to the published results of conservative treatment(Table 2.1) and were achieved even though all patients in his series had involved axillary lymph nodes and many had advanced disease at presentation. An era had began of radical surgery for breast cancer and surgery was to become even more radical in the early and mid parts of the twentieth century. Halsted extended his operation to include a supraclavicular node dissection in combination with the radical mastectomy but abandoned this due to an increased operative morbidity and the observation that there was no survival advantage. Urban(1952) described an en-bloc (or in-continuity) resection of the internal mammary chain in combination with the radical mastectomy and Wangensteen(1949) described the supra-radical mastectomy combining radical mastectomy with supra-clavicular node dissection, median sternotomy and resection of both internal mammary chains. However, both these procedures were associated with an increased morbidity without improvement in survival.

The Halsted radical mastectomy became the "gold standard" treatment for breast cancer for much of the early and mid-part of this century. This radical approach to breast cancer treatment was based on the thought that breast cancer metastasised by means of the lymphatic system and that eradication of that system not only gave an improved local control but an improvement in overall survival. This theory was really an over-simplification and paid little emphasis to the problem of venous spread. Although some surgeons such as Urban at Memorial Sloan Kettering in New York advocated operations such as the extended radical mastectomy many became disillusioned by radical surgery and reports appeared of less radical forms of mastectomy.

In 1948 David Patey, a surgeon at the Middlesex Hospital, London published his results of a lesser form of mastectomy than the Halsted operation which became known as the Patey mastectomy(Patey and Dyson, 1948). In this procedure pectoralis major was left behind and the pectoralis minor muscle excised in order that a full axillary dissection could be performed. The local relapse free survival for the radical mastectomy was 76% compared to 82% for the modified operation. The operation became modified further by

Madden(Madden et al 1972) who advised leaving both pectoralis major and minor muscles behind in the so called modified radical mastectomy. Surgical practice gradually changed with a move away from the Halsted operation toward the Patey or the modified radical mastectomy as described by Madden. A survey of American Surgeons conducted by The American College of Surgeons in 1982(Wilson et al, 1984) and compared to a similar survey carried out in 1977 found an increase in the use of the modified radical operation(from 55.6% in 1977 to 78.2% in 1982) and a move against Halsted's operation(from 27.5% in 1977 to only 3.4% in 1982).

Whilst extending the radical mastectomy to include the supra-clavicular or internal mammary nodal areas was felt to be acceptable surgical practice and the less radical Patey mastectomy became fashionable any lesser procedure was felt to be most unacceptable and indeed negligent. A leading article in the British Medical Journal in October 1953(Anon) summed up the current feeling on the subject :-

"*So firmly established had the practice of radical mastectomy become that even to question its value smacked of lese majeste , and those who had the courage to look for other methods had to face, not only the barriers of reasoned resistance, but an array of prejudice which lifted the discussion out of the cool atmosphere of scientific argument and plunged it into a cauldron seething with emotion*".

Even before 1953 there were people who seriously questioned the value of the radical mastectomy operation. The absolute cure rate was low and there was definite morbidity in the form of arm oedema and limitation of movement at the shoulder associated with the procedure. An early sceptic was Professor George Gask at St. Bartholomew's Hospital, London who in 1922 initially instigated Mr.Geoffrey Keynes to investigate the use of radium needles to treat recurrent breast cancer. Encouraged by the results he obtained he extended the use of radiotherapy to patients with advanced breast cancer and then to treat early breast cancer. He even undertook simple tumour excision and followed this with breast radiotherapy. Another early advocate of the use of

conservative surgery in combination with radiotherapy was M. Vera Peters a radiotherapist at St. Margarets Hospital in Toronto who started this form of treatment as far back as 1939.

Apart from Keynes and Peters few people practised conservative surgery for breast cancer. However, a few reports started to emerge in the 1950's to support the use of a more conservative approach. Mustakallio(1954) reported an 84% five year survival in 127 patients with clinical stage one breast cancers treated by local excision and radiotherapy and Sir Arthur Porritt(1964) from St. Mary's Hospital, London described a personal series of patients treated by conservative surgery and radiotherapy with promising results. These reports were largely anecdotal arising from non-randomised retrospective studies and it was not until 1972 that the safety of a more conservative surgical approach combined with radiotherapy was reported by Atkins et al at Guy's Hospital.

2.1.2 Trials comparing mastectomy and breast conservation

In 1955 Sir Hedley Atkins et al considered the hypothesis that radical mastectomy was no more effective in preserving life in cases of early breast cancer than simple lumpectomy. The first prospective randomised trial comparing radical mastectomy and wide excision followed by radiotherapy(in this paper wide excision was referred to as extended tylectomy which was defined as removal of the tumour with a 3cm rim of surrounding normal breast tissue) began to accrue patients in 1961 at Guy's Hospital. Three hundred and seventy six patients were entered and randomised to radical mastectomy and post operative radiotherapy or to extended tylectomy without axillary dissection followed by post-operative radiotherapy both to the breast and nodal areas. Both groups were well matched for age(all were over 60 years old) tumour size etc. By the time the first paper appeared in (Atkins et al, 1972) it was evident that there were serious problems with the tylectomy group. Statistical analysis revealed that in the clinical stage II group radical mastectomy gave significantly better survival than extended tylectomy(60% vs 28% at 10years), however in the clinical stage I group there

was no significant difference in survival. Local recurrence was significantly better for the radical mastectomy group for clinical stage I and II patients. Clear interpretation of the results was difficult, the radical mastectomy group had received axillary surgery and axillary radiotherapy whereas the tylectomy group received only axillary radiotherapy, furthermore the radiotherapy doses given were certainly inadequate by today's standards. However, it emerged from the data that the survival in the clinical stage I group was similar and this then encouraged a second study comparing radical mastectomy and tylectomy in the clinical stage I group only. A further 252 patients were accrued between 1971 and 1975 but surprisingly the group treated by conservation fared worse both in terms of relapse free and overall survival(Hayward 1985).

The differences in the results between the two trials were at first difficult to explain. Hayward and Caleffi(1987) in a subsequent analysis were able in part to explain the differences by the observation that there were a greater number of smaller (T_1)tumours in the second series and that the T_2 group in the second series fared similarly in terms of local control and overall survival. It was in the T_1 group in the second series that the major differences emerged, the patients in this group treated by mastectomy had significantly better relapse free and overall survival than the tylectomy group. The lessons concluded from the Guy's studies were that surgery was capable of cure for small lesions and that inadequate local treatment led to an increased incidence of local relapse and an inferior overall survival. For lesions larger than 2cms(i.e.T_2 cancers) the inference was that loco-regional therapy might not be as important as systemic therapy in affecting long term overall survival.

Two other prospective randomised clinical trials began in 1972 and in 1973. The first which started in 1972 was organised by the Institut Gustave-Roussy, Villejuif, France(Sarrazin et al, 1984) and accrued 179 patients between 1972 and 1980. Criteria for entry to the trial were patients with unilateral breast cancers 2cm or less on macroscopic examination, aged less than 70 years. Pregnant patients with breast cancer were excluded. Randomisation was to simple mastectomy or local tumour

excision(tumour excision plus a margin of 2cms of glandular tissue) plus breast irradiation. Both groups underwent a low axillary dissection and those with positive nodes underwent a full axillary dissection. This latter group were then randomised further to receive postoperative nodal irradiation or no nodal irradiation. One hundred and seventy nine patients were entered into the first trial, 88 randomised to tumourectomy and 91 to mastectomy. When mastectomy was compared to tumourectomy there was no significant difference in overall or relapse free survival. These results were confirmed at 10 years of follow up(Sarrazin et al, 1989), furthermore 92% of patients treated by tumourectomy had either an excellent or a good cosmetic result.

In 1973 another trial was set up by the Istituto Tumori in Milan under the auspices of Professor Umberto Veronesi. Seven hundred and one patients with breast cancers less than 2cms in diameter without palpable axillary nodes were randomised to either Halsted radical mastectomy or to quadrantectomy, axillary dissection and breast radiotherapy. Patient accrual took place between 1973 and 1980 and those found to have positive nodes after 1976 received CMF adjuvant chemotherapy. At 5 years of follow up(Veronesi et al, 1981) there was no difference in disease free or overall survival. Only one patient in the quadrantectomy group developed a local recurrence. The balance in breast conservation surgery lies in the "trade off" between performing a wide excision leading to a low local recurrence rate and an inferior cosmetic result versus a narrower excision, a better cosmetic result but a higher local failure rate. Veronesi et al(1981)achieved a low local recurrence rate but almost 1 in 3 of his patients had an inferior cosmetic result(Fentiman, 1990). At a median follow up of 13 years (Veronesi et al, 1990) overall and disease free survival remained identical.

Probably the most referenced paper confirming the safety and efficacy of breast conservation as an alternative to mastectomy are the published results of the National Surgical Adjuvant Breast Project, a multi-centre trial known as the NSABP B06 trial(Fisher et al, 1985). Patients with breast cancer, up to 4cm in diameter were

randomised to one of three treatment groups:- total mastectomy or segmental mastectomy with or without breast irradiation. All patients underwent an axillary dissection and patients with positive lymph nodes received systemic adjuvant chemotherapy. Those who received breast irradiation were given a dose of 50 Gy without a boost to the excision site. Patients treated by segmental mastectomy who had positive tumour margins on histological examination were converted to total mastectomy but remained in their original randomisation group when comparisons were made of survival i.e. the randomisation was an intention to treat rather than actual treatment. Over eighteen hundred patients were entered into the trial between 1976 and 1984. The mean follow up was only 39 months(range 5-99) and the disease free survival, distant disease free survival and overall survival were similar in all three groups. The local recurrence rate in the breast of those patients treated by segmental mastectomy and irradiation was 8% at 5 years compared to 30% for those treated by segmental mastectomy alone and in this latter group local recurrence rose to 36% in those with positive axillary nodes. Breast irradiation significantly reduced the incidence of local recurrence($p<0.001$). Logical assumption would therefore suggest that disease free survival would be reduced in the segmental mastectomy group but the protocol of the study stated:-

"*The occurrence of tumour in the breast after segmental mastectomy was not considered an event in the disease free survival of a patient, since patients who underwent total mastectomy as their initial operation were not at risk for the occurrence of a breast tumour*".

Therefore according to the protocol of the NSABP B06 trial it was possible to develop a local recurrence in the ipsilateral treated breast but this was not considered to constitute a reduction in the disease free survival. Other features worth noting were that 10% of patients in the segmental mastectomy group had positive tumour margins and were converted to mastectomy. The follow up at eight years confirmed the 5 year findings(Fisher et al, 1989) and further follow up(Fisher et al,1991) showed that by 9 years the local recurrence rate had risen in the segmental mastectomy and irradiation group from 8% to 12% and from 30% to 43% in the non-irradiated group. At nine years

of follow up(Fisher et al, 1991) even though a high proportion of those treated by segmental mastectomy without irradiation had developed an isolated breast recurrence their distant disease free survival was no different from the segmental mastectomy and irradiation or from the total mastectomy group. But a Cox's regression analysis of the lumpectomy group revealed that those patients who developed a local recurrence were at 3.41 times greater risk of developing distant disease and also, the development of an early local recurrence carried a less favourable distant disease free survival. They concluded that the development of an isolated breast recurrence was a marker of an increased risk of, but not a cause of, distant metastases. Local recurrence will be discussed in greater detail below.

The clear messages from the NSABP B06 trial were that segmental mastectomy with clear pathological margins, axillary clearance and breast irradiation was a safe alternative to mastectomy for tumours of 4 cms or less and that segmental mastectomy alone leads to an unacceptably high local recurrence rate. Other prospective studies have confirmed the safety of breast conservation and an overview of these studies and the studies presented in this chapter are outlined in table 2.2

Trial(author)	Treatment arms	No. Patients	Follow up(yr)	Local Relapse(%)	Survival(%)
Guy' s	Rm + Rt	186	10	14	60
(Atkins, 1972)	Le + Rt	190		68	28
Guy' s	Rm + Rt	130	10	8	68
(Haywood, 1987)	Le + Rt	122		30	58
Milan	Rm	349	13	2	69
(Veronesi, 1990)	Quart	352		3	71
NSABP B06	Mrm	590	8	8	71
(Fisher, 1989)	Le+Ad+ Rt	636		6	71
	Le+ Ad	629		16	76
Gustave-Roussy	Mrm	91	10	10	80
(Sarrazin, 1989)	Le+Rt+Ad	88		6	79
NCI	Mrm	116	5	10	85
(Lichter,1992)	Le+Rt+Ad	121		17	89

Table 2.2:- Randomised trials to assess efficacy of conservative surgery compared to mastectomy(from Sacks and Baum, 1993)

Rm=Radical mastectomy, Mrm= Modified radical mastectomy, Rt=Radiotherapy, Le=Local excision, Ad= Axillary dissection,

Quart= Quadrantectomy, axillary dissection and radiotherapy.

To conclude, the work reviewed in this chapter so far has shown how the treatment of breast cancer has essentially done an about turn in the last 100 years having moved away from an era of treating breast cancer conservatively in the late 1800's through a radical era and now into an era where several studies with good statistical correlation have shown that conservative surgery combined with radiotherapy in appropriately selected patients is a safe alternative to mastectomy.

2.1.3 Breast conservation

2.1.3a Introduction and patient selection

The above trials have outlined the safety of breast conservation, but the technique is only of proven efficacy for selected patients e.g. those with tumours less than 4 cms in diameter. It would be worthwhile at this point identifying which patients are and which are not suitable for breast conservation.

The upper size limit considered suitable for breast conservation is 4cms, without signs of local advancement, extensive nodal involvement or distant metastases. Many patients with smaller tumours would not be suitable for conservation because of small breast size resulting in a poor cosmetic result and are best treated by mastectomy possibly with immediate reconstruction. Central tumours were not initially considered suitable but are not a complete contra-indication to conservation, the nipple is lost but the general shape remains. Multi-focality is considered a contra-indication to conservation as it leads to a high incidence of local recurrence(Kurtz et al, 1990). Breast conservation has been shown to be safe for tumours other than invasive ductal carcinomas(Kurtz et al, 1989) but is not suitable for the treatment of inflammatory carcinomas.

The safety of this technique for treating early carcinomas such as Ductal Carcinoma in Situ(DCIS) has yet to be fully established and is currently the subject of a nationwide U.K. study. Early results from an NSABP Study(Fisher et al, 1993) comparing 818 patients with DCIS randomised to segmental mastectomy with or without irradiation have found a significant improvement in "event free survival"(subsequent tumour at a

local, regional or distant site after the initial operation) in the irradiated breast group even at 43 months of follow up. The presence of an extensive in-situ component in association with an invasive ductal carcinoma appears to predispose patients to an increased risk of local recurrence and these patients are possibly not suitable for conservation(see below). Age is not a contra-indication to conservation but young patients(<35 years) appear to have an increased incidence of local recurrence(Recht et al ,1988). Elderly patients are suitable for conservation provided that they are treated in a conventional manner by lumpectomy, radiotherapy and tamoxifen(Dixon, 1992). Pregnant women with breast cancer are best treated either by modified radical mastectomy or if the pregnancy is terminated by conservation followed by radiotherapy. Patients with connective tissue disorders are not suitable. The final barrier to breast conservation is patient choice. Some patients opt for mastectomy rather than conservation even after counselling(Wilson et al, 1988) The reasons why some patients choose mastectomy rather than conservation are varied. In addition, some patients are advised to undergo mastectomy by their surgeons even if they have small carcinomas(see chapter 5). In the U.K. there is a regional variation in the treatment of breast cancer with mastectomy being advised more frequently in certain parts of England(Harries et al, 1993).

2.1.3b Cosmetic appearance

The cosmetic appearance following conservative surgery and radiotherapy is an important consideration. The art of successful breast conservation is to achieve a good cosmetic result without compromising local control. Large resections especially in a small breast lead to poor cosmesis. The Milan group(Veronesi et al, 1981) were able to produce a low local recurrence rate but the procedure of quadrantectomy lead to a poor cosmetic result in nearly 1 in 3 patients(Fentiman, 1990).

Sarrazin et al(1984) used the operation of tumourectomy combined with axillary dissection and radiotherapy, local relapse was 6% at 10 years and 92% had a satisfactory cosmetic appearance. Radial incisions in the breast give an inferior

cosmetic result as does using the same incision for tumourectomy and axillary dissection(Sacks and Baum, 1993). Although the cosmetic appearance following surgery is usually evident within weeks or months following treatment, the time course for radiotherapy changes is more protracted. Some authors(Harris et al, 1991) have suggested that a minimum of three years is required to adequately assess the cosmetic appearance and that the cosmetic appearance stabilises at three years with only minor changes thereafter. High dose radiotherapy(>50 Gy) leads to poor cosmesis as does large daily fraction doses >2Gy. The simultaneous administration of chemotherapy and radiotherapy is also thought to give a poor cosmetic appearance(Sacks and Baum, 1993).

Patient acceptability

Given the choice not all patients, even if they are suitable, opt for breast conservation. The reasons are many and varied and include a fear of recurrence in the conserved breast. There is little evidence that those patients who undergo conservation have a lower psychological morbidity than those who undergo mastectomy. Fallowfield et al(1986) found no difference in psychological morbidity in those undergoing conservative treatment or mastectomy and even suggested that those with conservation may experience more anxiety due to the possibility of local disease recurrence.

2.1.3c Local recurrence following breast conservation and radiotherapy

The development of local recurrence following breast conservative surgery and radiotherapy is a well recognised problem. Local recurrence is defined as:-

" *The clinical appearance of progressive cancer within the parenchyma or skin of the breast, occurring at some time after macroscopically complete primary tumour excision and standard megavoltage whole breast radiotherapy* "

(Kurtz, 1992)

It is important here to differentiate a true recurrence or a so called "marginal miss" from the development of a new cancer at a site remote from the original excision bed.

The incidence of local recurrence varies from less than 1%(Veronesi et al, 1981)for the operation of quadrantectomy and from 2%(Bartelink et al, 1988) to 21%(Locker et al, 1989) at 5 years for the operation of lumpectomy. The incidence increases with time and is said to occur at 1.5% per annum(Kurtz et al, 1989). The local recurrence rates in the NSABP B06 trial rose from 8% at 5 years(Fisher et al,1985) to 12% at 9 years(Fisher et al, 1991). Other studies with longer follow up have quoted local recurrence rates of 7% at 5 years, 14% at 10 years and 18% at 15 years(Kurtz et al,1989). This study also found that the majority of local recurrences(79%) occurred in the vicinity of the tumour bed. The factors contributing to the development of a local recurrence within the breast can be subdivided into three sections; patient related, tumour related and treatment related factors.

Patient related factors

The majority of studies which have looked at young age have found an increased risk of local recurrence in younger women with breast cancer(Kurtz, 1992) Table 2.3 summarises the local recurrence rates related to age in two large series, the median follow up in the Joint Centre for Radiation therapy, Harvard(JCRT) series was 8.5 years and in the Marseille series 11 years(from Kurtz, 1992).

What is evident from the following data is that the local recurrence rate is approximately 3-8 times higher in women less than 35 years when compared to women older than 65 years. The reasons for this difference are not known but it is of interest that younger women have a higher incidence of an Extensive Intraduct Component(EIC) within their tumours(Harris, 1991, Jacquemier et al, 1990). EIC and its relationship to local recurrence is discussed in more detail later in this section.

	Local failure(%)	
Age range(years)	JCRT	Marseille
<35	24%	18%
35-50	13%	13%
51-65	10%	9%
>65	3%	7%

Table 2.3: Local recurrence rates as a function of patient age, based on the treatment of T1 and T2 tumours treated at the Joint Centre For Radiation Therapy(JCRT, Boston) and at Marseille(from Kurtz,1992).

Harris et al(1991) in an update of the JCRT data found that 31% of women aged 34 or younger had an EIC positive tumour compared to 18% for women older than 66 years and Jacquemier et al(1990) found EIC positive tumours in 29% of women under the age of 35 compared to 10% in those older than 60 years. The increased incidence of EIC in younger women cannot completely explain the higher incidence of local recurrence in younger women since the early analysis of the JCRT data(Recht et al, 1988) found an increased incidence of breast relapse in younger women who had EIC negative tumours when compared to older women with EIC negative tumours at a median follow up of 63 months.

Recht et al(1988) argued that there was a tendency to do more limited surgery in younger patients in order to achieve a better cosmetic result and that this lead to a greater residual tumour burden. Other thoughts put forward were that patient age was related to differences in the biologic behaviour of breast cancers or related in some way to circulating oestrogens having an effect on residual cancer foci. Whatever, the balance of evidence suggests that those patients who may wish most to preserve their breasts are at a higher risk of local failure.

A single study of 324 patients cited by Kurtz(1992) has indicated a higher local failure rate in women with small breasts(14%) compared to women with larger breasts(2%); this was thought to be due to be related to the volume of excised breast tissue in conjunction with the tumour i.e. more normal tissue could be excised in larger breasts.

Tumour related factors

Tumour location, the presence or absence of skin dimpling or nipple retraction and axillary nodal involvement have not consistently been shown to predispose to a higher incidence of local recurrence. In fact, in terms of axillary nodal involvement most series have shown fewer local failures in node positive patients, attributable most probably to the use of adjuvant systemic chemotherapy(Kurtz, 1992). There is no evidence at the present time that hormone receptor status has any influence on the likely development of a local recurrence(Fisher et al, 1991).Tumour size has not been found to be associated with an increased risk of local failure in the majority of studies which have looked at this variable(Kurtz, 1992).

Breast conservation is suitable for tumours other than invasive ductal carcinomas. Lobular carcinoma has not been implicated as a significant causual factor in local recurrence in the larger series. In a series of 67 patients with invasive lobular carcinoma treated by conservation and radiotherapy(Kurtz et al 1989) the local failure rate was 13.5% for invasive lobular cancers compared to 9% for invasive ductal cancers at 5 years(non-significant) and similar local control rates of 12% for lobular cancers and 11% for ductal cancers have been reported by the JCRT at 5 years(Schnitt et al, 1989) although only 49 patients with invasive lobular cancer were included in this study. The Nottingham group(du Toit et al, 1991) in a study of 171 patients with lobular carcinoma, 27 of whom were treated by local excision and irradiation, found an increased incidence of local recurrence in the lobular compared to the non-lobular group treated in a similar fashion($p<0.05$) at a median follow up of 64 months and another study by Mate et al(1986) from Yale which only included 12 patients with lobular cancer found a local recurrence rate of 25%($p=0.053$) which was significantly higher

than that found when compared to other histological types at a median follow up of 6.9 years. Information on the safety of conservation surgery for tumours other than invasive ductal tumours and invasive lobular cancers is sparse. In the Kurtz et al (1989) study mentioned above, 27 patients with medullary cancer and 11 patients with colloid cancers were included with local recurrence rates of 4% in the former group and no recurrences noted in the latter group.

The presence of an extensive intraduct component(EIC) within an invasive carcinoma is associated with an increased risk of local failure in the majority of series that have looked at this variable. An EIC is defined as " a locally excised infiltrating ductal carcinoma in which intraduct carcinoma accounts for at least 25% of the palpable tumour and is associated with an intraduct carcinoma in more than six low power fields of adjacent grossly normal breast tissue"(Sacks and Baum, 1993). An overview of local recurrence rates when tumours are considered to be EIC +ve or EIC -ve is illustrated in table 2.4. Results are presented from 5 centres which have all shown that the presence of an EIC significantly increases the risk of subsequent local relapse and data from Nottingham confirm these findings(Locker et al, 1989). Data from two centres, The Insitiut Gustave-Roussy(Clarke et al, 1985) which only analysed 22 patients with local recurrence with or without EIC and the NSABP data(Fisher et al, 1986) have not found EIC to predict local recurrence. This is most probably due to differences in the definition of EIC, the possible interactions of EIC with resection margins and the effect of age on the incidence of EIC.

Whatever, the majority of studies have found EIC to be an accurate predictor of subsequent local recurrence. The reasons put forward for this are firstly that EIC is relatively radioresistant(Anon, 1985) and secondly , evidence exists from 2 very good studies that the presence of EIC is an important marker of residual disease in the remainder of the breast. The first of these studies by Schnitt et al(1987) examined pathologic material in 71 patients with infiltrating ductal carcinoma treated by gross tumour excision and then selected for re-excision either because of EIC or tumour close

to, or at, the margins of excision. Residual carcinoma was seen in 62% of patients, 88% of those with an EIC had residual disease compared to 48% without an EIC. The second study by Holland et al (1990) who serially sectioned mastectomy specimens found "prominent" residual intraductal carcinoma in 44% of EIC +ve tumours compared to 3% of EIC-ve tumours. It is not surprising therefore that local recurrences are higher in these patients. Thirty three percent of patients with an EIC +ve tumour had "prominent" residual intraductal carcinoma 2cms from the edge of the primary tumour compared with 2% of patients with EIC -ve tumours. However, Holland et al (1990) found that the majority of the residual cancer was adjacent to the primary tumour rather than scattered throughout the breast suggesting, in theory, that a wider excision may reduce the higher incidence of local recurrence in patients with an EIC +ve tumour. Support for this theory comes from a study by Vicini et al(1991) who found that the local recurrence rates for patients with an EIC +ve tumour which were less than 2 cms in diameter were 29% for a "small" excision, 22% for a "medium" excision and 10% for a "large" excision. The adequacy of excision and its relationship to local recurrence is discussed below.

Centre(author)	No.Patients	Local Recurrence EIC +	EIC -	Follow up(yrs)	p value
Amsterdam *(Bartelink,1988)*	585	9%	2%	6	0.005
Boston *(Recht,1988)*	703	33%	8%	10	0.0001
Paris *(Fourquet,1989)*	518	23%	5%	10	0.03
Marseilles *(Kurtz,1990)*	496	18%	8%	5	0.001
London *(Lindley,1989)*	272	22%	10%	6	0.05

Table 2.4 : Local recurrence rates correlated with the presence or absence of EIC from 5 centres

High grade tumours appear to have a higher incidence of local recurrence in the majority of series that have examined this variable(Locker et al, 1989, Kurtz et al, 1990, Lindley et al, 1989, Clarke et al, 1985).Three series from Marseilles(Kurtz et al 1990), Yale(Mate et al, 1986) and The Westminster Hospital(Lindley et al, 1989) all found that the presence of necrosis within the tumour correlated with an increase in local recurrence. Lymphatic and vascular invasion have also been correlated with a higher local recurrence in several series(Mate et al, 1986, Fourquet et al, 1989, Locker et al 1989)

Treatment related factors

The amount of adjacent breast tissue excised at the time of lumpectomy undoubtedly influences the local recurrence rate. The study by Vicini et al(1991) supports this, even when the tumours were EIC negative the local recurrence rate was 9% for "small" excisions and zero for "larger" excisions. The local recurrence rates in the Milan series was 4% at 10 years using the operation of quadrantectomy compared to figures as high as 21% using the operation of lumpectomy(Locker et al, 1989). Veronesi et al(1990) in a prospective trial comparing quadrantectomy and lumpectomy(both groups had a full axillary clearance and received post operative breast radiotherapy) found a local recurrence rate of 7% for the lumpectomy group and 2.2% for the quadrantectomy group. So it appears that the wider the margins of excision the lower the local recurrence rates but this is achieved at the expense of cosmesis(Veronesi et al,1990).

Assessment of pathological margins is now routinely performed by most pathologists. Positive resection margins were found in around 10% of cases in the NSABP B06 trial(Fisher et al, 1985) and 16% for patients treated by tumourectomy and 3% for patients treated by quadrantectomy in the study by Veronesi et al(1990). An overview of the local recurrence rates and their relationship to margin status from 13 worldwide centres is presented in table 2.5.

Centre	No.patients	Follow up(months)	Local recurrence when margins +ve	-ve	p value	Comments
Duke *(Anscher,1993)*	259	44	9%	1.5%	0.01	only 11 local failures
New York *(Ghossein,1992)*	503	84	10.5%	12%	0.75	↑ DXT if margins +ve
Villejuif *(Clarke,1985)*	436	60	10%	5%	N.S.	
Marseille-Basle *(Kurtz,1990)*	586	71	24%	8%	0.0001	specimens not inked margins assessed retrospectively.
Los Angeles +ve. *(Ryoo,1989)*	393	92	13%	6%	0.19	↑ DXT if margins +ve margin defined as tumour within 5mm.
Pennsylvania *(Solin,1991)*	697	61	2%	7%	N.S.	↑ DXT if margins +ve
Richmond *(Schmidt-Ullrich,1989)*	108	60	0	0	N.S.	↑ DXT if margins +ve

Table 2.5: Local recurrence rates and margin status from 13 centres(continued overleaf)

Centre	No.patients	Follow up(months)	Local recurrence when margins +ve	-ve	p value	Comments
Chicago *(Hallahan,1989)* recurrences	216	36	6%	2%	not stated	↑ DXT if margins +ve only 7 local
Institute Curie *(Zafrani,1989)*	434	103	24%	9%	0.0001	specimens not inked
Milan *(Veronesi,1990)*	283	not stated	13%	5%	not stated	
Nottingham *(Locker,1989)*	140	96	45%	30%	N.S.	figures worked out from graphs.
Amsterdam *(Bartelink ,1988)*	274	72	10%	3%	0.02	figures worked out from graphs.
Leuven *(Van Limbergen,1987)*	238	97	20.2%	10%	0.04	

Table 2.5: Local recurrence rates and margin status from 13 centres

There are considerable problems in drawing any firm conclusions from these studies; most of these studies are retrospective containing differing numbers of patients; some series have not reported any local recurrences(Schmidt-Ullrich et al, 1989). Furthermore, the definition of what constitutes a positive resection margin varies from one centre to another. Most centres define a positive margin as tumour present at an inked resection margin, however, the series from Los Angeles (Ryoo et al, 1989) considered a positive margin to constitute tumour present within 5mm of the inked resection margin whilst others have not routinely inked their resection margins(Kurtz et al, 1990). Also, the presence of a negative resection margin does not definitely indicate that there is no tumour left behind in the breast. If re-excision takes place when margins are postive then between 55%(McCormick et al,1987) and 69%(Schnitt et al, 1987) of cases residual carcinoma is found in the breast. When margins are negative and re-excision takes place then somewhere between 26%(Frazier et al,1989) and 33%(Schnitt et al, 1987) of patients will have residual carcinoma in the breast. These figures confirm that inking of the resection margins will not always accurately predict complete tumour excision.

Even allowing for all these imperfections a cautious overview of the data presented in table 2.5 from the 13 centres indicates that:- 5 centres have reported a significant increase in local recurrence rates if the margins of excision are involved(Duke, Marseille-Basle, Institute Curie, Amsterdam and Leuven), 5 have reported a non-significant increase in local recurrence rates despite the fact that increased doses of radiotherapy were given to the tumour site if the excision margins were involved in 2 centres(Villejuif, Los Angeles, Chicago, Milan and Nottingham), 3 centres have reported similar local control rates but all gave increased doses of irradiation to the positive margins group(New York, Pennsylvania and Richmond). This data would then suggest that on the balance of available evidence, positive excision margins lead to an increase in the local recurrence rate and secondly, the evidence that this increase can be counteracted by increased doses of radiotherapy is far from conclusive. Little surprise then that surgeons faced with the question of what to do if the histological margins

were involved with tumour following a lumpectomy gave a wide variety of responses(see chapter 5).

The timing of radiotherapy may influence the local recurrence rates. A study from the Intitute Gustave Roussy (Clarke et al, 1985) reported loco-regional failure which was significantly increased in patients who began radiotherapy more than 7 weeks after definitive surgery. Certainly the dose of radiotherapy delivered is an important factor as can be seen from the Guy's study where inadequate radiotherapy led not only to a high local recurrence rate but also to a poorer overall survival(Atkins et al, 1972). The use of a boost of 10-15 Gy to the excision site reduced local recurrence from 13% to 7% in a Canadian study cited by Kurtz(1992). Whether radiotherapy can be spared in some patients with small or special type carcinomas is at present uncertain and is the subject of a prospective trial organised by the British Association of Surgical Oncology(BASO).

Finally the use of adjuvant chemotherapy or adjuvant tamoxifen is associated with lower local recurrence rates. The NSABP B13 and 14 studies have addressed the question of local recurrence with chemotherapy and tamoxifen respectively and early results suggest lower local recurrence rates in the treatment arms(Harris et al ,1991). However longer follow up will be necessary to confirm these early findings.

Local recurrence: Survival and treatment

The significance of the development of a local recurrence in terms of survival has been mentioned above. The study by Fisher et al(1991) found that the development of a local recurrence was a marker and not a cause of distant disease and that the development of an early local recurrence resulted in a poorer distant disease free survival. Chauvet et al(1990) found overall survival was reduced in patients who developed a local reccurence following conservative surgery and radiotherapy, others have found the development of an isolated recurrence did not adversely affect survival(Clarke et al, 1985). Kurtz et al(1989) found that the development of a local

recurrence within 24 months was associated with a poor prognosis but that prognosis after late recurrences(after 5 years) was favourable(84% 5 year survival).

Local recurrences are traditionally treated by mastectomy which offers good local control(88% at 5 years) compared to further breast conservation which gives local control rates of 64% at 5 years(Kurtz et al,1989).

2.1.4 The treatment of the axilla

Although the main purpose of this thesis is to examine the use of a new technique which may replace lumpectomy, no discussion on the treatment of localised breast cancer would be complete without discussing the management of the axilla. The management of the axilla is probably one of the most controversial subjects in breast disease. The axilla, receiving the majority of the lymphatic drainage from the breast, is the primary site for metastases from breast cancer. The presence or absence of axillary metastases is probably the most reliable indicator of prognosis(the axilla is discussed in more detail in chapter 3) and in addition approximately 40-50% of patients presenting with breast cancer will have axillary lymph node metastases(Henderson, 1990). Essentially three schools of thought exist regarding the management of the axilla(the case for all three opinions is put forward in a thorough review article by Sacks et al, 1992).

The first school of thought puts forward the case for total axillary clearance; this procedure provides excellent local disease control with local axillary recurrence rates of 1% or less. Complication rates in terms of arm morbidity and lymphoedema are similar to that following axillary radiotherapy. A full clearance to level III of the axilla allows a full assessment of the number of involved lymph nodes which in turn gives an idea of the overall survival(see chapter 3). This then allows rational decisions regarding adjuvant therapy. The knowledge of the patient's axillary status provides useful information for the clinician and for clinical trial and audit purposes.

The second school of thought believes that axillary sampling will give sufficient information about nodal status and allow rational decisions regarding adjuvant therapy. The value of sampling is controversial but has been shown to provide useful prognostic information by the Nottingham and Edinburgh groups(Sacks et al, 1992). The idea that sampling will provide good information without the complications of a full axillary clearance is as yet unproven. Certainly the use of sampling followed by axillary nodal irradiation can lead to an increased risk of arm lymphoedema.

The third school believes that axillary surgery is unnecessary. Proponents of this school argue that sensible decisions can be made without knowledge of axillary nodal status especially in post-menopausal patients who will be likely to receive tamoxifen regardless of nodal staus. An increasing number of node negative women are being offered chemotherapy although the survival benefits are not so great as they are for node positive patients, however the newer chemotherapy regimes produce moderate side effects which are well tolerated by many patients. In view of these two statements it is possible to treat patients without knowledge of axillary nodal status. Axillary radiotherapy has similar local axillary recurrence rates and similar complications to axillary clearance and thus provides good axillary disease control.

Each of these three schools have their proponents and views are often fiercely fought. Sacks et al(1992)from the Royal Marsden Hospital believe that axillary clearance should be undertaken in all pre-menopausal patients. They question the place of axillary surgery in the treatment of impalpable disease or for ductal carcinoma in situ(DCIS). They feel that axillary clearance should be undertaken at the time of mastectomy in all patients. In post-menopausal patients who are suitable for conservative surgery they feel there is a real choice. Either a full clearance can be undertaken or the axilla can be left alone and the patient be given axillary radiotherapy at the same time as they undergo breast radiotherapy. This management option is one of many. Surgeons opinions with regard to the management of the axilla can be found in the chapter on the survey of the management of breast cancer in England and Wales(Chapter 5).

2.2 Radiotherapy

The value of radiotherapy following lumpectomy has been discussed above. The purpose of this section is to briefly review what is known about the use of radiotherapy as a primary treatment for early breast cancer.

Primary radiotherapy can be used to treat breast cancer without surgery. However, the doses necessary to achieve tumour destruction are of the order of 60- 70 Gy. a dose which causes an unacceptably poor cosmetic result. Van Limbergen et al(1990) recently reported the use of radiotherapy without surgery in 221 women with T_{1-3} N_{0-1} M_0 breast cancer and concluded that radiotherapy was no longer an alternative to tumour excision and postoperative radiotherapy in most women because the high radiation doses necessary to achieve good local control lead to a poor cosmetic result. The doses needed to provide local control rates similar to those obtained after tumourectomy and irradiation are 10Gy higher for T1 and 35Gy higher for T2 tumours(Van Limbergen et al 1990)

2.3 Chemo-endocrine therapy

Introduction

The use of systemic chemotherapy and endocrine therapy as an adjuvant treatment for early breast cancer are beyond the considerations of this chapter which is concerned with the treatment of localised breast cancer. However, both primary chemotherapy and endocrine therapy have been used to treat the primary tumour with varying success.

Endocrine therapy

Tamoxifen has been used as the sole treatment for early breast cancer mainly in elderly women following reports in the early 1980's from non-randomised clinical trials(Preece et al, 1982, Bradbeer and Kyngdon, 1983, Allan et al, 1985) that tamoxifen alone was an effective treatment. However several trials have now compared the use of tamoxifen alone either with surgery alone or with tamoxifen and surgery. Two trials compared

tamoxifen alone with surgery alone. The first by Gazet et al(1988) found that tamoxifen was effective as a sole agent in elderly women. This study has been criticized(Dixon 1992) due to its small numbers, large proportion of inoperable tumours and because those randomised to surgery underwent wide excision only. The second study by Robertson et al(1988) randomised elderly patients to either wedge mastectomy and excision of affected axillary nodes or tamoxifen alone. Significantly more patients receiving tamoxifen required a change of management due to progression of disease.

Bates et al(1991) reported what has become known as the 'C.R.C. Golden Oldies' trial, a multicentre trial comparing tamoxifen alone versus tamoxifen and surgery(either lumpectomy or mastectomy) in 354 patients. At a follow up of 34 months there was an excess of local treatment failures in the tamoxifen group but no difference in overall survival. A further follow up at 42 months with 434 patients available for analysis(Bates et al, 1992) revealed a small but significant survival advantage for the surgery and tamoxifen group. Furthermore, those patients who had a lumpectomy had a five times higher rate of local recurrence within the breast than those treated by mastectomy. Another trial conducted at Guy's Hospital(Fentiman 1990) randomised patients to either modified radical mastectomy or tumourectomy and tamoxifen. The local recurrence rate(at a median follow up of 4 years) was 25% in the tumourectomy/tamoxifen group as opposed to 5% in the modified radical mastectomy group. The available evidence points to the fact then that tamoxifen is inadequate treatment on its own for elderly patients with breast cancer and that elderly breast cancer patients should be treated in the same manner as younger patients(Dixon 1992). However , some studies have recently reported the use of tamoxifen in oestrogen receptor positive patients(Low et al, 1992) and it may be that these patients are suitable for tamoxifen treatment alone, however further studies are awaited.

Chemotherapy

The use of primary(or so called neo-adjuvant) chemotherapy is a novel approach to the treatment of early breast cancer. Primary chemotherapy was used in the 1970's to achieve tumour shrinkage in stage III cancers but has recently been applied to the treatment of resectable breast cancer in order to achieve tumour shrinkage so that the patient may undergo conservative surgery rather than mastectomy. In a review article Bonadonna et al(1991) updated the Milan experience of treating 227 breast cancer patients with pre-operative chemotherapy. The degree of tumour response was inversely proportional to the initial tumour size. Complete pathologic remission was documented in only 4% of cases but 91% of patients with tumours over 3cms were able to have conservative surgery rather than mastectomy. In addition, 73% of patients with tumours >5cms in diameter underwent conservation. With a median follow up of 18 months from surgery plus post-operative radiotherapy, only 1 local recurrence was noted. Bonadonna et al(1991) cite a French study which randomised 272 patients with operable breast cancer greater than 3cms in diameter prospectively randomised to primary chemotherapy followed by loco-regional treatment versus mastectomy and adjuvant chemotherapy in high risk patients(node positive and node negative, ER negative tumours). Conservation was possible in 63% of patients treated by primary chemotherapy. At a median follow up of 34 months overall survival(but not relapse free survival) was improved in the primary chemotherapy group. Another advantage of using primary chemotherapy is to assess the response to chemotherapy and possibly to reduce the chances of stimulating the kinetics of metastatic cancer cells by excising the tumour(DeWys, 1972). The use of primary chemotherapy is at present in the stages of early development and the subject of many ongoing clinical trials.

CHAPTER 3: PROGNOSTIC FACTORS IN EARLY BREAST CANCER

3.1 Introduction

The overall five year survival for patients with breast cancer is approximately 75%. However, of the five year survivors a further 17% will die of their disease in the next five years(Young, 1989). If the clinician has an indication of the potential prognosis for a patient with breast cancer he can then counsel the patient appropriately and target patients with a poorer prognosis who would benefit from adjuvant systemic therapy. Conversely, he may be able to identify patients with a good prognosis who can be spared additional therapy. McGuire(1989) has estimated that if all patients with early breast cancer were treated with adjuvant systemic therapy, to achieve a disease free survival benefit for 5,040 patients, 64,960 patients would have to be treated, 59,920 patients therefore being treated unnecessarily. It is therefore important that those patients with a worse prognosis are identified and treated appropriately. It is worthwhile looking at the prognosis of untreated breast cancer which will give us an indication of the natural history of the disease and establish a baseline against which different treatments can be judged.

The natural history of untreated breast cancer was reported by Bloom and Richardson et al(1962) who reviewed 250 patients who had attended the Middlesex Hospital in London between 1805 and 1933. The median survival from the onset of symptoms was 2.7 years, 18% survived to five years and only 4% to ten years.

The prognosis for a patient with breast cancer will depend on many factors which can be broadly divided into two categories, patient related factors and tumour related factors.

3.2 Patient related factors

3.2.1 Patient Age

Age as a prognostic factor in breast cancer has been investigated in several studies with discordant results. One of the largest studies by Host and Lund(1986) studied the influence of age on survival in an unselected series of 31,594 patients with breast cancer reported to the Norway Cancer Registry and found the most favourable prognosis in the 35-49 age group and poorest in patients older than 75 years and younger than 34 years. This trend was present for all stages of the disease.

There is little evidence to support the view that breast cancer is a less aggressive disease in the elderly(Host and Lund, 1986, Fentiman, 1990) leading some authors to conclude that they should be managed in the same way as younger patients(Dixon, 1992).

3.2.2 Pre morbid Weight

Several studies have indicated an unfavourable prognosis in obese patients with breast cancer(Boyd et al, 1981) even after adjustment for stage. In a more recent study by Treteli et al(1990) from the Cancer Registry of Norway a total of 8,427 patients with breast cancer were followed up for an average of 4.3 years. Height and weight were measured prior to diagnosis. Among those patients with stage I disease the death rate was 1.7 times higher in obese patients(as measured by the Quetelet index namely weight in Kilograms divided by Height in centimetres squared) than in slim patients and 1.42 times higher in patients with stage II disease. Obesity was not a prognostic factor for patients with stage III or IV disease. There are several possible explanations for these findings. If obesity does act as a prognostic factor the mechanism is said to involve increased conversion of the precursor androstenedione to oestrone by aromatase(found in adipose tissue) and thence stimulation of oestrogen dependent breast cancer(De Waard et al, 1981). Obese women tend to have low levels of sex binding globulin, a specific protein which binds and transports oestradiol, this in turn makes oestradiol available to peripheral tissues for biological interactions.

These findings may be explained by the suggestion that obese patients in the node negative group may have had a preponderance of larger tumours which are known to have a worse prognosis(Carter et al,1989).Support for this theory comes from Treteli's study where there were larger tumours in the obese patients than in leaner patients in the stage I group. Boyd et al(1981), however, found that the prognostic effect of weight could not be explained by differences in clinical stage using the TNM classification or histological grade of the tumour.

3.2.3 Breast cancer during pregnancy

Between 10 and 39 cases of breast cancer are diagnosed per 100,000 pregnancies(Saunders and Baum, 1993). Because breast cancer during pregnancy is rare studies correlating breast cancer and pregnancy tend to contain small numbers of patients.

Petrek et al(1991) from Memorial Sloan-Kettering in a retrospective study identified 56 patients with pregnancy associated breast cancer (defined as breast cancer occurring during pregnancy or within 1 year post partum) and compared them with non pregnant women of comparable ages treated by the same physicians during the same time period.The pregnancy associated breast cancer patients were more likely to have positive axillary nodes than the control group (61% vs 38%), however the five year survival was similar in the two groups for stage I(82%) and stage II(47-59%) patients. Nugent and O'Connell(1985) also found a trend toward a more advanced stage at diagnosis in pregnant women when compared to controls but when stage was taken into account there was no significant difference in overall survival.

3.2.4 Timing of surgery in relation to menstrual cycle.

There has been a lot of interest recently regarding the prognosis for a patient with early breast cancer in relation to the timing of surgery. Following an initial observation in mice of a correlation between the stage of oestrous at which a primary breast cancer was resected and the likelihood of later pulmonary metastases, Hrushesky et al(1989)

performed a retrospective study of 44 women who underwent resection of a primary breast cancer and noted a worse prognosis for patients operated during days 0-6 and 21-36 of their menstrual cycles. Badwe et al(1991) in another retrospective study of 249 patients from Guy's hospital noted a reduced overall and recurrence free survival in patients operated on during days 3-12 of their cycle. These findings were broadly in agreement with the findings of Senie et al(1991) from Memorial Sloan Kettering who also found a higher recurrence rate among those operated on during the follicular phase(up to day 14). Powles et al(1989) analysed data on 81 patients and Gelber and Goldhirsh(1989) data on 245 patients and were unable to reproduce the findings of Hrushesky or Badwe, indeed Sainsbury and Round(1992) in a retrospective study of 142 patients found a better prognosis for patients operated on between days 3-12 and call for a nationwide prospective study(currently being organised by the Yorkshire breast cancer group) before operative policies are changed.

3.2.5 Psycho-social factors

The relationship between psychological adjustment to the development of breast cancer and adverse life events following diagnosis and their effect on prognosis have been investigated in several studies. A prospective study of 57 women with early breast cancer(Pettingale et al,1985) showed that patients who coped with their disease by means of a positive attitude were more likely to be alive and free of disease at 10 years. Severely threatening adverse life events(such as death of a loved one or divorce) were shown to be significantly associated with early relapse in 50 patients with breast cancer in a case controlled study by Ramirez et al(1989). However, in a larger study involving 204 women followed prospectively, Barraclough et al(1992) was unable to give support to the theory that psychological stress contributed to relapse of breast cancer.

3.3 Tumour related factors

3.3.1 Tumour size

Increasing tumour size is associated with an increased probability of positive nodes as well as a higher risk of recurrence and death. The reports from the Surveillance, Epidemiology and End Results(SEER) Program of the National Cancer Institute (Carter et al,1989) analysed data on 24,740 breast cancer patients and showed a decreasing survival in node negative patients with increasing tumour size.The five year survival was 99.2% for patients with tumours less than 0.5cm decreasing to 82.2% for patients with tumours greater than 5 cms.The incidence of positive axillary lymph node metastases steadily increased from 20.6% in patients with small tumours (<0.5cms) to 70.1% for patients with tumours greater than 5 cms.

In a recent prospective study of 1392 patients with breast cancer who were treated by modified radical mastectomy(Crowe et al, 1992) tumour size in a Cox's proportional hazards model was a significant predictor of disease free and overall survival when the number of positive nodes, oestrogen receptor status, menopausal status and race were considered.

3.3.2 Lymph node status

The commonest sites of regional node involvement are the axillary , supraclavicular and internal mammary nodes.The presence and number of involved lymph nodes are probably the most important predictor of overall survival.

Axillary node involvement

Between 40 and 50% of patients with a tumour evident on clinical examination have axillary nodal involvement(Henderson,1990) although clinical examination of the axilla is notoriously inaccurate in predicting axillary node metastases with false positive rates of the order of 25-29% and false negatives in the region of 27-32% (Bucalossi et al,1971, Haagenson,1986, Schottenfield et al,1976).

The incidence of axillary node metastases is higher if the tumour is placed laterally rather than medially or centrally in the breast(Nemoto et al, 1980), furthermore the likelihood of axillary nodal involvement is directly related to the size of the tumour(Carter et al, 1989) both of which are directly related to overall survival. The ten year survival is directly related to the presence or absence of axillary nodal metastases. Several series have reported ten year survival figures of 65-80% for node negative patients and 25-48% for node positive patients (Haagenson, 1977, Fisher et al, 1975, Valagussa et al, 1978) The prognosis is not only related to the presence or absence of axillary metastases but also related to the number of nodes involved. Haagenson (1977) found that the ten year survival for patients with 1-3 nodes involved was 63% compared to 27% if greater than 4 nodes were involved. Nemoto et al(1980) analysed the prognosis in greater detail with an analysis of 7,634 node positive patients. By analysing the prognosis in relationship to the number of involved nodes, the 5 year survival for patients with one involved node was 63% decreasing to 22% if more than 21 nodes were involved.

Although node negative breast cancer is generally thought to carry a favourable prognosis, between 20 and 35% of these patients will be dead by 10 years, the reason why some patients survive and others do not may be related to the size of the tumour, or to the grade or it may be that some of the so called node negative patients have been wrongly labelled as such. The prognosis for these patients who were thought to be node negative but on more thorough pathological examination of axillary nodes were found to be node positive has been investigated in several series. Wilkinson et al(1983) studied 525 patients who were thought to be node negative, 89(17%) were subsequently found to be node positive. However patients with and without occult metastases had similar five year survival rates. The results of this study are at variance with the results of a larger study by the International(Ludwig) Breast Cancer Study Group(1990). By more thorough histological examination of 921 axillary nodes excised in the course of mastectomy and axillary dissection 83(9%) were found to have occult micrometastases. The five year survival of these patients was significantly worse than those whose nodes

remained negative on serial sectioning. Axillary nodal metastases from breast cancer then are an important predictor of prognosis, the likelihood of nodal metastases is influenced by the site of the tumour and the prognosis is related not only to the presence but also to the number of involved axillary lymph nodes.

Internal mammary node involvement

Veronesi et al(1985) analysed his data on 1119 patients who had undergone internal mammary node dissection. Metastases to the internal mammary nodes were found to be significantly associated with the maximum diameter of the tumour(16% for tumours less than 2cms, 24% for tumours >2cms) and patient age.There was a strong association between internal mammary involvement and axillary lymph node metastases(29% of patients with positive axillary nodes had internal mammary node involvement compared to 9% when axillary nodes were negative). In this study survival was significantly affected by the presence of positive internal mammary nodes, ten year survival was 80.4% when both internal mammary and axillary nodes were negative compared to 30% when both sites were involved and 53% when the internal mammary nodes were involved alone.

Supraclavicular node involvement

Halstead (1907) performed supraclavicular node dissections in 119 patients, 45 were found to have supraclavicular node involvement and only 2 (4.4%) were disease free at 5 years. The subsequent development of supraclavicular nodal metastases also carries a poor prognosis being strongly associated with the development of distant metastases (Fentiman et al, 1986).

3.3.3 Histological sub-types

Approximately 65-80% of breast carcinomas can be categorized as invasive ductal adenocarcinomas and 10-14% as invasive lobular carcinomas. Other tumours are relatively uncommon such as tubular, medullary, mucinous, cribriform and papillary carcinomas each constituting between 1-5% of invasive breast carcinomas(Harris et al, 1991)

Invasive ductal adenocarcinoma

Bloom and Richardson (1957) described a method of assessing histological and nuclear grade of invasive ductal adenocarcinomas. Despite likely inter-observer variability(Gilchrist et al,1985), which may account for discordant reports of the relationship between grade and prognosis, the system has been widely accepted by pathologists in the United Kingdom. Several studies have shown a correlation between high grade and poorer overall survival in both node negative and node positive patients. Tumour grade was assessed in 1537 patients in a study by Davis et al(1986), the overall survival was 86% for grade I, 70% for grade II and 57% for grade III. Tumour grade remained a statistically significant prognostic factor for overall survival in a multi-variate analysis after controlling for nodal status, tumour size, oestrogen receptor status, menopausal status, age and peritumoral vessel invasion.

Peritumoral lymphatic emboli have been implicated in a poorer overall survival in several studies analysing node negative patients(Clemente et al, 1992) but the significance of lymphatic invasion for node positive patients is less certain. Rosen et al(1989) found no difference in survival at 10 years for node positive patients with lymphatic invasion but Davis et al(1986) found a significantly worse prognosis in a similar trial at 5 years. The presence of vascular invasion defined as penetration by tumour into the lumen of an artery or vein has also been associated with a poor prognosis in some series (Weigand et al, 1982).

Lobular Carcinomas

Lobular carcinomas can be subdivided into five groups, classical, alveolar, solid, tubulo-lobular and mixed. Ellis et al(1992) in a recent review of 243 patients with lobular carcinoma found an overall survival advantage for these patients when compared to ductal adenocarcinomas. When the tumours were divided into their subgroups there was a highly significant difference in survival. Classical, tubulo-lobular and lobular mixed tumours had a significantly better prognosis than ductal carcinomas but solid lobular carcinomas had a similar prognosis to ductal carcinomas. These results confirmed the findings of Dixon et al(1982) who found a survival advantage for lobular carcinomas with a similar distribution of subtypes in an analysis of 103 patients.

Lobular carcinomas are said to have a different distribution of metastases showing a propensity to metastasise to the meninges, peritoneum and retroperitoneum whilst pulmonary metastases were more commonly associated with ductal carcinomas (Harris et al,1984). Dixon et al(1991) compared 72 patients with metastatic ductal carcinomas and compared these with 77 patients with metastatic lobular cancer. He was able to confirm Harris's findings of a different clinical spread of metastases to the liver and peritoneum but was unable to demonstrate a significant difference in pulmonary or meningeal metastases. Dixon et al(1991) also showed a significant survival advantage for patients with metastatic lobular carcinoma when compared to patients with metastatic ductal carcinoma.

Tubular Carcinomas

Tubular carcinomas account for no more than 2% of invasive breast cancers although the frequency of this tumour is said to be higher in a screen detected population(Royal College Of Pathologists Working Group,1990).This tumour is generally thought to have a favourable prognosis. Ellis et al(1992) analysed 38 patients with this subtype and found a significantly better survival when compared to ductal carcinomas with a 90% 10 year survival. A good prognosis for this type of tumour has also been reported by other workers(Peters et al, 1981).

Cribriform carcinomas

Invasive cribriform carcinomas account for 2-4% of invasive breast carcinomas. Due to the fact that this tumour is relatively rare most series linking invasive cribriform carcinomas with prognosis contain relatively small numbers of patients. Page et al(1983) analysed 35 patients with pure cribriform carcinomas. At follow up of 10-21 years none of these patients had died of their disease. Ellis et al(1992) were able to confirm Page's findings of an excellent prognosis in the 13 patients that they studied.

Mucinous Carcinomas

Mucinous(or colloid) carcinomas constitute 1-2% of breast carcinomas.This tumour is also considered to be prognostically favourable but due to its rarity, series of patients with mucinous carcinoma are often small. Ellis et al(1992) described a 10 year survival of 80% and similar figures have been obtained in other series(Clayton,1986). Patients with mucinous carcinomas are reported to have a tendency to develop metastases a long time after treatment of the primary tumour(Rosen and Wang,1980). Tumour size and nodal status are the main indicators of prognosis in this group of patients.

Medullary Carcinomas

Ridolfi et al(1977) found an 84% 10 year survival for medullary carcinomas compared with 58% for invasive ductal carcinomas with atypical medullary carcinomas having an intermediate prognosis. Some workers have not found a favourable prognosis for medullary carcinomas(Pedersen et al, 1988) and this has lead Ellis et al (1992) to conclude that medullary carcinomas should be placed in a moderate rather than a good prognostic group.

3.3.4 Steroid Hormone Receptors

Many studies have indicated a better prognosis for breast cancer patients whose tumours are oestrogen receptor positive rather than oestrogen receptor negative (Elledge et al, 1992). McGuire et al(1990) reviewed data from San Antonio analysing 2028 patients and the NSABP data analysing 825 patients. Disease free survival was improved by the

order of 8-10% for ER positive patients. The reasons for these differences are not clear, some authors have suggested that this difference may be due to the increased likelihood of ER positive tumours to respond to endocrine treatment rather than some intrinsic biological factor of the tumour(Howell et al,1984), however this theory fails to hold true if you analyse other studies of patients treated without adjuvant treatment. Pearson et al(1985) in an analysis of 510 patients with stage I breast cancer treated by mastectomy without adjuvant therapy found patients with low ER levels(<3fmol/mg) had a worse disease free and overall survival than those with higher ER levels(>3fmol/mg), this analysis was for postmenopausal patients but for premenopausal patients ER negative patients did worse than ER positive patients in the first two years but survival in the two groups was similar after three years. Other workers have indicated that the favourable prognosis for ER positive tumours is not sustained with longer follow up and suggest that ER positivity is related to the growth rate of the tumour rather than to its metastatic potential (Mason et al, 1983).

Progesterone receptors have also been studied with regard to prognosis with conflicting results. McGuire et al(1990) found progesterone receptors not to be of prognostic significance in an analysis of 2028 patients whilst others have found positive progesterone receptors a stronger predictor of survival than positive oestrogen receptors.(Sigurdsson et al, 1990)

3.3.5 Cell Kinetics and Ploidy

In recent years there have been a large number of publications on DNA flow cytometry and breast cancer. The quantity of DNA within the cell(DNA ploidy) and, using suitable mathematical modelling, the percentage of cells undergoing active DNA synthesis(S-phase) can be measured using the technique of DNA flow cytometry. The technique is based on the measurement of fluorescence from dyes which bind in a stoichiometric fashion to DNA.

O'Reilly and Richards(1992) in a recent review article on DNA flow cytometry looked at 11 studies concerning S-phase fraction and DNA ploidy.The number of patients in these studies varied from 140 to 690. On univariate analysis there was evidence of an association between high S-phase fraction and shorter relapse free survival in 3 studies and reduced survival in 5 studies. Patients with aneuploid tumours also tended to have a poorer prognosis than those with diploid tumours(in 6 studies). However, multivariate analysis was not able to support the ability of DNA ploidy to provide independent prognostic information.

Whilst it is generally accepted that node positive patients have a worse overall survival than node negative patients approximately 16% of node negative patients will die of their disease within 5 years. With recent evidence suggesting a survival benefit for patients receiving chemotherapy(Early Breast Cancer Trialists Collaborative Group,1992) much interest has been focused on DNA ploidy and S-phase fraction to see if these techniques could identify the 16% of patients with a poorer prognosis.There appears to be little evidence of an independent prognostic role for DNA ploidy although there is evidence of an independent prognostic role for S-phase fraction in some, but not all, studies(O'Reilly and Richards, 1992).

3.3.6 C-erb B2

C-erb B2(or HER-2/neu) is a proto-oncogene. The protein product of this oncogene is a membrane bound receptor molecule with tyrosine activity. Slamon et al(1987) studied expression of C erb-B2 in 189 breast tumours. A two to thirty fold amplification was found in 30% of cases and this was related to a poorer survival in node positive but not node negative patients. This discovery subsequently led to further studies some of which confirmed(Walker et al, 1989) whilst others(Barnes et al, 1988) were unable to confirm Slamon's findings.

In an analysis of the NSABP B06 data Paik et al(1990) demonstrated, not surprisingly, a good prognosis for node negative women with good nuclear grade. However on further analysis of the specimens those patients whose tumours expressed C erb B2 had a five fold increase in mortality. Cerb B-2 expression may be useful in identifying patients who are node negative who are at a higher risk of recurrence who could be offered appropriate adjuvant therapy. However the usefulness of this oncogene has yet to be fully established.

3.3.7 Cathepsin D

Cathepsin D is a lysosomal acidic protease. The cathepsin D levels were studied in 199 node negative and 198 node positive patients by Tandon et al(1990). The levels for cathepsin D in normal breast was below 8 units and the median cathepsin D levels from patients with node negative tumours was 36 and from node positive patients 69 units. In node negative patients higher levels of cathepsin D was associated with a shorter disease free survival and overall survival. The five year survival for patients whose tumours had high levels of cathepsin D was 55%, significantly less than the 80% five year survival when levels were below 75 units. Tandon was unable to demonstrate a similar effect in node positive patients. Thorpe et al(1989) studied cathepsin D levels in 242 premenopausal and 154 postmenopausal breast cancer patients. A lower level of cathepsin D was again correlated with a better disease free survival in pre and post menopausal patients. In this study an improvement in disease free but not overall survival was evident in node positive and node negative patients. Spyratos et al(1989) have demonstrated that patients with positive nodes and low levels of cathepsin D had a better prognosis than patients who were node negative and had high levels of cathepsin D. It appears then that cathepsin D is a reliable prognostic indicator but again further studies are needed before its place is fully established.

3.3.8 Other factors

A number of other factors such as epidermal growth factor and the protein ps2 have also been correlated with prognosis. Tumours which have been found to be epidermal

growth factor receptor positive have been associated with a poorer prognosis in some series(Sainsbury et al,1987). Ps2 is a protein which when present in a tumour has been associated with a longer disease free and overall survival (Foekens et al, 1990) in some series, its expression is under the control of oestrogen but its exact function is unknown.

3.4 A prognostic index

The preceding discussion details the many factors which govern the prognosis for a patient with breast cancer. The problem for the clinician is how to interpret this information and get an overall picture of the prognosis in order to counsel the patient and be able to make rational decisions about adjuvant therapy. In 1982 Haybrittle and Blamey et al outlined a prognostic index which they described as:

Prognosis = 0.2 x size of the tumour(cms.) + Stage + Grade

The stage was designated a number 1-3 depending on the degree of nodal involvement and the grade 1-3 according to the Bloom and Richardson classification.The index gives a score for good(<3.4), moderate(3.4-5.4) and poor(>5.4) prognosis. The score of good prognosis correlates with a 5 year survival of 88% compared to 69% for the moderate group and 21% for the poor prognosis group. The index was able to identify a group of patients in the good prognostic group who were node negative, with grade 1 tumours less than 20mm in diameter whose score was below three and had a prognosis similar to women of the same age without breast cancer. The prognostic index has been confirmed by the Nottingham group at eight years of follow up(Todd et al,1987).

3.5 Summary

It is important to know the prognosis for a patient who has developed breast cancer firstly to counsel her appropriately and secondly to target patients with a poorer prognosis who would benefit from adjuvant therapy. There are many factors that will govern the prognosis for a patient the most important of which are tumour size, lymph node status and tumour grade. A prognostic index has been worked out incorporating all these factors and allows sensible decisions about adjuvant treatment.

CHAPTER 4 : INTERSTITIAL LASER PHOTOCOAGULATION

4.1. Introduction

Surgery is often used to remove tumours together with a rim of adjacent normal tissue in order to ensure good local tumour control and in some cases to cure the disease. With the advances that have occurred in non invasive imaging techniques in recent years it is now possible with a fair degree of accuracy to map out the full extent of the tumour and with the aid of newer techniques such as MRI to obtain good soft tissue resolution or with colour flow doppler an indication of the vascularity of a tumour. At the same time that these imaging techniques have evolved a deeper understanding of tumour biology has lead to the belief that in at least some cases local destruction of tumours together with a rim of normal tissue is all that is necessary surgically to achieve local control and that the metastatic potential of many tumours have been predetermined before the patient presents to the clinician. Therefore, taking the concept of conservative surgery for cancer a step further, is there another way of causing local tumour destruction utilising the advances in imaging techniques to accurately guide the mechanism of local destruction to the tumour and hopefully predict the amount of tumour destruction?

The purpose of this chapter is to review what is known about the principles, experimental and clinical work regarding interstitial laser photocoagulation, a new minimally invasive technique capable of safe *in-situ* tissue destruction.

4.2. Hyperthermia

The idea of using heat to treat tumours is not new. In the Edwin Smith Surgical Papyrus(Breasted, 1930) which has been carbondated to 1700 BC there is an account of the treatment of breast cancer with a firedrill. The haemostatic and tissue destroying properties of heat were also used widely by the Greeks and Romans. Hyperthermia has been induced systemically in an attempt to achieve tumour destruction. This was based on an observation by Busch in 1866 who noted that a histologically proven facial sarcoma disappeared after two attacks of erysipelas associated with high fever. Coley in 1893 deliberately induced hyperthermia by injection of bacterial pathogens in an attempt to destroy tumours. Other methods of achieving whole body hyperthermia in

an attempt to raise the core body temperature to 41-42°C have used water blankets and hot air cabinets. Prolonged treatment at these temperatures can result in irreversible hepatic and cardiac damage and have hence largely fallen into disuse. The use of heat to treat tumours focused then onto more localised treatments aimed at local destruction of the tumour with minimal systemic upset to the patient. Microwaves, radiofrequency and ultrasound have all been described but all have their limitations (Bleehen, 1982).

4.3. Lasers

The word laser is an acronym for **L**ight **A**mplification by **S**timulated **E**mission Of **R**adiation. Although the principle of laser action was described by Einstein in 1917 it was not until 1960 when Maiman described the first working ruby laser. A Laser is a sophisticated source of elecromagnetic radiation producing light which has the properties of monochromacity, collimation and coherence. Laser light can be transmitted down thin flexible fibres and is therefore an ideal tool for surgical, endoscopic or percutaneous work.

The wavelength emitted from the laser depends upon the active medium within it and this material can be a solid, a liquid or a gas. A wide spectrum of wavelengths can be produced ranging from light in the ultraviolet range (<400nm) e.g. The Excimer laser through the visible spectrum(400-700nm) e.g.the Helium Neon laser to the infrared(>700nm) e.g. the diode laser at 805 nm, the Nd:YAG laser at 1064 nm and the Holmium:YAG at 2080nm in the near infrared spectrum to the $C0_2$ laser in the far infrared spectrum at 10,600nm. Continuous wave lasers have three principle effects in medicine, high power thermal, low power thermal and photodynamic or photochemical effects. The purpose of this chapter is to concentrate on what is known about the low power thermal effects.

4.4. Principles of Interstitial Laser Photocoagulation(ILP)

The concept of interstitial laser photocoagulation was first described by Bown in 1983. Thin flexible optical fibres are inserted into the target organ percutaneously via thin hollow needles. The fibre tip lies bare within the tumour. The laser is then activated at low powers(up to 3watts) with long exposures(300-1000 seconds). The laser light is absorbed as heat in the tissue resulting in slow heating and, as more energy is dissipated, tissue denaturation, water vapourization and eventually coagulative necrosis occur. The resultant necrosis was predictable and roughly spherical in shape around the tip of the laser fibre. There was little in the way of damage to the surrounding normal tissue. The area heals by resorption and eventually forms a hard fibrous nodule. Bown(1983) showed how this technique was capable of local destruction in a subcutaneous metastasis from a bronchogenic carcinoma. The technique had great potential in tumour destruction, the laser allowed a predictable volume of necrosis with no damage to surrounding tissue and the fact that the light could be passed down thin optical fibres made virtually any organ in the body accessible to this technique. Clearly before the technique could be put forward clinically it had to be evaluated experimentally.

4.5 Delivery systems

Laser light is delivered to a tissue via thin optical fibres which can range from 0.1 to 1mm in diameter. These usually comprise of a central core of high quality material which can be fused silica or glass. Fused silica fibres are suitable for transmission of light of wavelengths of 220-1300nm whilst glass fibres are suitable for transmission of light of wavelengths of 380-1300nm. The inner core is coated with a thin layer of material at a slightly lower refractive index(the so called cladding). The cladding can also be made of silica which has an impurity such as fluorine added to it in order to lower the refractive index or the cladding may be made of glass or a polymer. The cladding is then surrounded by an outer jacket usually made of plastic. Light is transmitted along the fibre by total internal reflection with minimal power loss and fibres can be made as long as required.

4.6 Laser-tissue interactions

Laser light can interact with biological tissues in a number of different ways. The light can be absorbed, scattered, reflected or transmitted through the tissue(Figure 4.1). The biological response of the tissue depends upon the light intensity of the laser, the wavelength of the laser and the optical properties of the tissue with which it interacts. Only absorbed light has a biological effect; reflected and transmitted light produce no biological effect but scattering of light causes it to be absorbed by a larger volume of tissue.

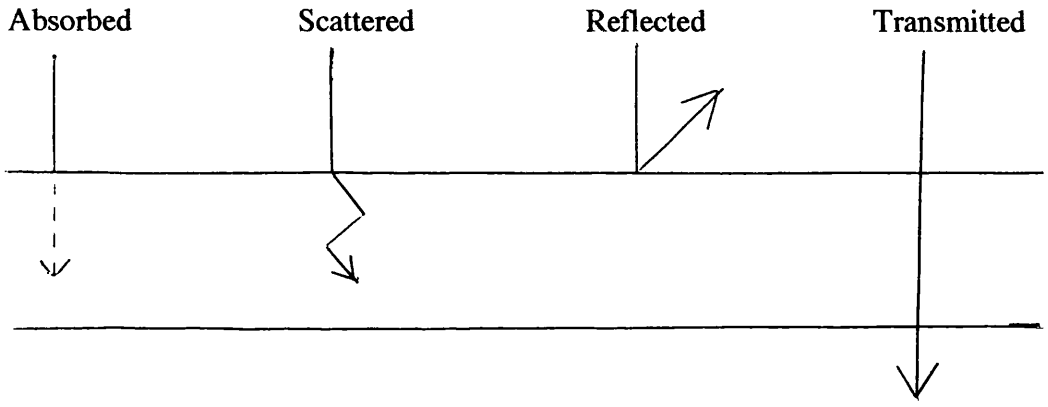


Figure 4.1: Laser light interacts with biological tissue in one of four ways.

As the wavelength increases through the visible portion of the spectrum into the near infra-red, the transmission of light through the tissue increases. The absorption of light will depend then upon the output wavelength of the laser. For example, the CO_2 laser with a wavelength of 10,600nm in the far infra-red aspect of the spectrum produces light which is strongly absorbed in water. This results in the deposition of a large amount of energy into a small area with little tissue penetration(to a depth of only 0.1mm in soft tissue). The CO_2 laser is therefore effective as a cutting tool but ineffective for ILP. The 1064nm Neodymium Yttrium Aluminium Garnet (Nd-YAG) laser has very good tissue penetrating properties and is highly scattered in tissue(Bown, 1983) and has long been thought of as probably the best laser for ILP although this

notion has recently been challenged(see below). The Argon ion laser has two wavelengths, 488nm and 514 nm and light is strongly absorbed in haemoglobin, hence the Argon laser is effective in destroying port wine stains. The 480nm pulsed dye laser is absorbed in the yellow carotenoid pigment in atheroma and has been used in laser angioplasty.

Once light of a particular wavelength penetrates biological tissue then it will be absorbed as heat and the distribution of absorption will be dependent upon the optical properties of the tissue. The optical properties of tissues vary from tissue to tissue and are dependent upon the biological constituents of that tissue. Optical properties will vary with the tissue vascularity(Jacques et al, 1992) and tissue inhomogeneities(Svaasand et al, 1985) and in addition recent evidence(Essenpreis et al, 1991) suggests that tissues are able to change their optical properties during ILP treatment. Although this has not been demonstrated in tumour tissue Essenpreis et al(1991) have demonstrated a change in the optical properties of post mortem bovine liver during ILP.

Once absorption occurs then the resultant tissue changes are dependent upon the temperature reached and the time for which the tissue remains at that temperature(Thomsen,1991). Thomsen(1991) has characterised thermal biological effects into three different thermodynamic processes. 1) Lower temperature thermal damage 2) Higher temperature effects dominated by water vapourisation and 3) High temperature ablation by tissue vapourisation, combustion and molecular dissociation.

At temperatures up to 40-45^{o} C reversible cell injury can occur depending upon the exposure that the tissue has to that temperature. At temperatures of 43-45C irreversible cell damage will occur after exposures ranging from 25 minutes to several hours depending upon the type of tissue(Thomsen, 1991). As the temperature increases from 45^{o}C up to 99^{o}C irreversible denaturation of proteins occurs and coagulation thermal effects are evident; coagulated cells shrink and their nuclei and cytoplasm become

dense. This is evident at light microscopy as nuclear pyknosis and celluar hyperchromasia, thermally damaged epithelial cells become elongated and spindled perhaps due to collapse of the cytoskeleton. The main difference between the irreversible cell death caused by higher temperatures and the reversible cell damage seen at lower temperatures is that in the former structural cellular damage is evident immediately after treatment whereas with the latter it may be 48-72 hours before the full extent of tissue damage is evident(Thomsen, 1991). As tissue temperatures approach the threshold temperature of vapourisation of water(100°C) tissue water(which accounts for about 80% of the constituents of soft tissue) boils resulting in steam bubble formation within the tissue(Brackett et al 1986), the bubbles enlarge and eventually rupture explosively resulting in mechanical disruption of cells. Steam escapes along tissue planes into adjacent blood vessels(a phenomenon which can be seen during ILP treatment when monitored in real time with ultrasound). Water strongly absorbs light at wavelengths over 1300nm with the water absorption peaks occuring at around 1450 and 1950nm in most tissues except fat(Blanc and Colles ,1990). In addition, the main determinant of the thermal conductivity of a tissue will be the tissue water content. Once the available tissue water dessicates then both the optical and thermal properties of the tissue change. The temperature rises rapidly up to 300-400°C resulting in carmelization, carbonisation and tissue combustion leading to cavitation, char formation and the production of smoke. The mechanisms of tissue ablation are not well understood but are probably due to thermal breakdown of tissue elements and molecular bonds(Thomsen,1991). Once charring has occured then obviously the transmission of light from the laser fibre into the surrounding tissue decreases significantly and the damage to the tissue occurs by means of thermal conduction with the fibre tip acting as a point heat source(Wyman et al,1992, Amin et al, 1993). The importance of charring is discussed in the section on the experimental work(see section 4.7.3).

It is clear then that the amount of necrosis produced when laser light interacts with a tissue depends on the optical penetration of the light into the tissue, the penetration

being dependent upon the optical properties of the tissue with which it interacts and the output wavelength of the laser.

4.7 Experimental work on ILP

4.7.1 Experimental work in normal tissue

The earliest experimental work on the technique of ILP concentrated on the use of single fibres in experimental animal models using the Nd-YAG laser which was thought, at that time, to have the best tissue penetration. Initial studies were carried out in normal tissue.

Mathewson(1987) et al in one of the earliest and widely quoted studies performed ILP in rat liver using low powers(0.5-2 Watts) with long exposures(up to 1000 seconds) and a single 400μm bare tipped fibre. They were able to demonstrate predictable areas of necrosis of up to 16 mm. The maximum diameter of necrosis plateaued at around 400-600 seconds. Charring around the fibre tip occurred with powers above 0.75 Watts and was thought of as being undesirable. A moderate fall in light intensity within the liver was noted at higher powers and was thought to be due to the production of char around the fibre tip. Mathewson et al(1987) also performed radiological studies on the hepatic arterial supply and were able to demonstrate loss of all small and some large vessels in the treated area. Histological examination of the treated area revealed a small, central, charred and cavitated area immediately adjacent to where the fibre had been and a larger diameter of necrosis surrounding this. These areas of thermal damage caused little or no general upset to the animals and in time the area healed by regeneration and fibrosis. Sixty days following ILP the thermally treated area was replaced by a small fibrous nodule. Further groups studied ILP at low powers (up to 4 watts) with exposures of 360 seconds using 600μm fibres in porcine liver(Dachman et al 1990) and were able to produce necrotic lesions up to 1cm in diameter. Matsumoto et al(1992) produced ILP lesions in rabbit liver again using a 600μm fibre and were able to produce necrotic lesions of up to 24mm in longitudinal and 15mm in transverse diameter at 3 watts with an exposure of 300 seconds by forward advancement of the laser fibre(3-

5mm) during treatment. Bosman et al(1991) described ILP in the livers of four pigs but with a variation in necrotic lesion size ranging from 10-15mm. ILP has been undertaken in other tissues apart from the liver. Schatz et al(1992) described the use of ILP in normal rabbit brain and again predictable necrotic lesions of 6-10mm could be produced with safety. All of these studies utilised a single bare tipped fibre.

For adequate tumour destruction in many tissues and to ensure good local control it is usually neccesary to destroy not only the tumour but a rim of normal tissue as well. This is certainly evident in breast cancers as we have seen in chapter 2 and is desirable in the treatment of hepatic metastases as well where a 10mm margin beyond the macroscopic deposit is advised by some authors(Greenway, 1988). A single fibre would be unable then to treat larger tumours ; the first option would be to perform several treatment cycles; another would be to use more than one fibre. The latter option has been explored by Steger et al(1992) who found that it was possible to produce lesions of up to 4 cms in diameter in normal canine liver using four fibres fired simultaneously from the Nd-YAG laser(using 200μm fibres). The use of a beam splitter enabled a power output of 1.5 Watts per fibre. The fibres were placed 1.5 cms apart and the laser activated for 670 seconds using 1.5 watts per fibre. Again, apart from one hepatic abscess developing one month after ILP(thought to be due to poor asceptic technique at the time of treatment) and minor changes in serum liver enzymes, few complications arose as a result of ILP and the areas healed safely by fibrosis and regeneration. McNicholas et al(1993) have recently described the use of multiple fibre ILP in the prostate of elderly beagles and described necrotic lesions of up to 26mm in diameter, again without significant post treatment complications.

Modifications to the bare fibre tip have been described and compared in several studies to the standard bare tip. The most frequently described modifications are a variety of ovoid and pointed tips made from sapphire, a ceramic material with a high melting point and greater tensile strength(Daikuzono and Joffe, 1985). Tissue charring is usually avoided by using flowing saline. Two studies have compared the diameter of necrosis

obtained during ILP using a bare tipped fibre and a contact sapphire probe. In one study using pig liver the bare fibre tip produced significantly larger lesions than the sapphire tipped fibre 2 weeks after ILP(Castren-Persons et al, 1992). Karanov et al (1992) similarly found a disadvantage to using a sapphire tipped fibre compared to a bare fibre in a study of implantable mammary tumours in mice. Many of these ovoid sapphire tips are too large to pass down the core of a hollow needle suitable for ILP use. Van-Eeden et al(1988) also showed that the diameter of necrosis produced in liver around a sapphire tip was less than that around a bare fibre for the equivalent laser powers and exposure times. Malone et al(1992) compared a plane cut bare fibre tip with cylindrical diffusing fibre-tips in porcine liver and found that the bare fibre tips produced more effective necrosis. Nolsoe et al(1992) described a diffuser tip made by stripping the cladding from the distal 1cm of the fibre and then grinding the distal 2-3mm of the fibre core to give a cone shaped frosted tip which emmited light in a spherical distribution. This modification was compared with the bare tipped fibres. In pig liver using 4 watts for 600 seconds necrotic lesions up to 44mm in diameter could be produced with the modified fibre compared to 15mm for the bare tipped fibres which produced cylindrical shaped lesions. Panjehpour et al(1990) also described interstitial hyperthermia(rather than photocoagulation) using a long(13mm) tapered frosted contact probe which showed promise but has not as of yet been compared to the bare tipped fibre.

An overview of this data would suggest that the early modifications of the fibre tip are in reality no better than using a bare fibre but recent modifications (Panjehpour et al, 1990; Nolsoe et al 1992) show some promise.

4.7.2 Experimental work in tumour models

One of the principle determinents of the final degree of laser induced necrosis is the optical properties of the tissue with which the laser light interacts. Many of the studies outlined above have been conducted in normal relatively homogenous animal tissue, yet tumour tissue is often inhomogenous containing areas of necrosis, haemorrhage and

having areas of disordered vascularity. Tumour tissue is in theory likely to behave in a different manner from normal tissue when it interacts with light and support for this comes from two studies looking at the optical properties of normal and neoplastic tissue. Nakamura et al(1990) were able to show a difference in the optical properties of normal and malignant human liver tumours and Key et al (1991)were able to demonstrate a difference in the optical properties of benign and malignant breast tissue. Several studies have now examined the use of ILP in experimental tumour models.

Mathewson et al(1989) performed ILP using a bare fibre in a transplantable fibrosarcoma in the flank of a rat. Those rats treated by ILP using 1200J had a significant survival advantage over controls or surgical excision. Karanov et al(1992) performed ILP in a transplantable mammary carcinoma in the flanks of mice and were able to show that 60% of the tumour was necrosed in the ILP group compared to 10% for controls(necrosis was due to spontaneous necrosis in the control group). Dowlatshahi et al(1992) used 5 watts and exposures up to 400 seconds in implantable mammary carcinomas in the flank of rats and were able to show a significant correlation between the volume of tissue necrosis and the level of laser irradiation(i.e. at an energy level of 500 Joules a mean volume of necrosis of $0.8cm^3$ was obtained compared to $4cm^3$ at an energy of 2,000 Joules). Dachman et al(1992) transplanted a VX2 carcinoma into the liver of rabbits and found necrotic lesions less than a centimetre in diameter after ILP.

4.7.3 Charring

The original description of ILP(Bown 1983), early experimental work (Mathewson et al 1987) together with the work of other authors(Panjehpour et al, 1990) have all suggested that charring should be avoided because it reduced light transmission into the surrounding tissues. Other authors(Dowlatshahi et al,1992) even went as far as saline cooling of the fibre tip in order to prevent charring. Wyman et al(1992) following observations of ILP in experimental bovine and chicken muscle suggested that charring was in fact advantageous. A recent study from our institution(Amin et al 1993a) has

examined the significance of charring and the value of using a pre-charred fibre. A significant association existed between the presence of charring and the size of necrosis in rat liver using clean bare tipped 400 μm fibres at 805, 1064 and 1320 nm's. The use of a pre-charred fibre was achieved by dipping the fibre tip into a drop of the rats blood and firing the laser at 4-5 watts for a few seconds so that the distal 3mm of the fibre tip was blackened. Pre-charring the fibre significantly increased the necrotic lesion diameter at a wavelength of 1064nm (even increasing the diameter of necrosis at 1 watt by a factor of 5.7)but not at the 1320nm wavelength where charring appeared spontaneously using a clean fibre at 15-60 seconds. Amin et a(1993) concluded that once charring occured a positive feedback began, with even less light penetrating resulting in higher local temperatures and more charring. Pre-charring the fibre simply allowed this cycle to be initiated at 1064nm with a dramatic increase in lesion diameter. When charring occurs the laser fibre tip essentially acts as a point heat source and the consequent necrosis occurs then by means of a purely thermal process (as outlined above), the extent of necrosis depending upon the temperature reached and the length of time that the tissue is subjected to that temperature(Thomsen,1991). Logically, one could question if lasers then have any advantage over other mechanisms which can produce a point heat source. Lasers still possess the ability to deliver a predictable amount of energy to a tissue and as the energy can be transmitted down thin flexible fibres they still have considerable advantages over other techniques.

4.7.4 Histological features of ILP in normal and tumour tissue

Mathewson et al(1987) described the histological features of ILP in rat liver. A central, cavitated, charred area was visible surrounded by an area of coagulative necrosis. At the junction between the necrotic area and viable normal liver an inflammatory infiltrate had developed. Four days after ILP granulation tissue was evident in the outer zone(i.e.the junction between the necrotic area and viable normal liver) together with groups of giant cells, proliferating bile ductules and isolated hepatocytes. In time, the area matured such that at 60 days a small hard fibrous scar remained at the centre of the necrosed area. Many of these histopathological changes have been described by other

authors(Matsumoto et al, 1992, Dachman et al, 1990, Bosman et al, 1991). Recently(Thurell et al, 1994) our group have described an area of apparently intact viable hepatocytes immediately adjacent to the central zone of cavitation and charring following ILP in rat liver. This area was surrounded by coagulative necrosis. Staining for NADPH diaphorase enzyme(a marker of the viability of the cell) has confirmed that these apparently intact cells are in fact non-viable. Schatz et al(1992) described histopathological features of ILP in rabbit brain describing a central zone of coagulative necrosis and haemhorrage, the tissue necrosis being more marked at 24-48 hours after ILP rather than immediately after treatment. Schatz et al(1992) also described an outer transition zone between the necrotic and viable brain tissue which contained neutrophils initially, followed by proliferation of capillaries and infiltration by microglial cells(a form of macrophage). One month after ILP in the brain ghost outlines of cells remained within the central zone of necrosis. At a cellular level, Thomsen(1991) described how thermally coagulated cells shrank and their nuclei exhibited nuclear pyknosis and hyperchromasia and described how thermally damaged cells became elongated and spindled in shape secondary to collapse of the cytoskeleton.. Thomsen(1991) described how thermally coagulated tissue damage was most evident immediately after treatment but other authors have found that this damage is more striking 24 hours or so later(Mathewson et al, 1987).

4.7.5 Lasers for ILP

The Nd-YAG laser at 1064nm is highly scattered in tissue and hence has excellent tissue penetrating properties(Bown, 1983) penetrating soft tissue for up to 6mm(Masters and Bown, 1990b). The Nd-YAG laser has always been thought of as being the ideal laser for ILP. The disadvantages of the Nd-YAG laser is that it is large in size, requires water cooling and a three phase electricity supply. Recently a small compact(about the size of a typewriter) high power, semi-conductor diode laser has become available(Diomed®, Cambridge Ltd.) which is lightweight, works off "mains" electricity and does not require water cooling. In addition a 1320nm Nd-YAG laser has recently been introduced. Amin et al(1993a) studied ILP in rat liver using the Nd-YAG

lasers at 1064nm and 1320nm and the diode laser at 805nm at 1, 2 and 3 watts at 1000, 500 and 333 seconds(i.e. using 1000 Joules in each case). The size of necrosis attained using a clean fibre with the 1064nm Nd-YAG laser was significantly smaller than the necrosis attained using the 1320 Nd-YAG or the 805nm diode laser. There was no significant difference in necrotic lesion diameter between the diode laser or the 1320 nm Nd-YAG laser. The value of spontaneous charring has been discussed above, charring occurred readily with the 805nm diode and the 1320 nm Nd-YAG laser but did not occur spontaneously with the 1064nm Nd-YAG laser. It appears from this study then that the 1320nm Nd-YAG and the 805nm diode lasers are more suitable for ILP than the conventional 1064nm Nd-YAG laser using a clean fibre but by precharring the fibre tip, the 1064nm laser can give similar results to the 805nm laser, i.e. wavelength is not important if charring is present.

4.8 Imaging of ILP

4.8.1 Introduction

Experimentally ILP looks promising but it is becoming clear that one of the major problems that will be encountered clinically is imaging; knowing exactly where the boundaries of the tumour are and matching the extent of laser necrosis to the full extent of the tumour. The perfect imaging technique will allow(a)accurate assessment of the margins of the tumour (b)accurate placement of laser fibres (c)real time monitoring of hyperthermic changes and (d)accurate prediction of the final extent of necrosis. Unless these criteria are met then ILP has limited potential as a minimally invasive technique for *in-situ* tumour destruction. Various non-invasive imaging techniques have been investigated principally ultrasound, Magnetic Resonance Imaging(MRI) and to a limited extent Computerised Tomography(CT).

4.8.2 Ultrasound

Ultrasound would be an ideal tool to meet the above criteria in that it is widely available, safe , portable and easy to perform at the same time and in the same room as ILP. Several groups have now studied the findings which occur during ultrasound

monitoring of ILP in real time and have correlated these findings with histology. Steger et al(1992) studied ultrasonic features of ILP in canine liver. Using a single fibre placed interstitially into canine liver at a power of 1-1.5 Watts for 670 seconds Steger et al(1992) were unable to see any changes for the first 20-30 seconds. This was followed by the sudden appearance of a hyperechoic star measuring 5mm in diameter. A 3mm hyperechoic ring then developed around the star . The hyperechoic star and the surrounding ring then gradually expanded for 300-400 seconds. There was no further expansion of this lesion after 400 seconds up until the end of treatment. During the initial 300-400 seconds echogenic foci suggestive of gas bubbles were evident radiating from the central white star and if these appeared within a vessel the bubbles were seen to"wash" away. The bubbles seen on ultrasound represent the bubbles formed during ILP in tissue at the point of vapourisation of tissue water and essentially represent small steam bubbles(Brackett et al, 1986). Steger et al (1992) found a good correlation between the sonographic and pathological measurements of ILP induced necrosis. Dachman et al(1990) also performed ILP in pig liver and monitored thermal changes with ultrasound. They described similar ultrasound appearances namely a well defined homogenous echogenic focus around the fibre tip although this area was maximal at the start of treatment and diminished in size. Subsequent ultrasounds over several weeks were able to record healing of the lesion; again good correlation with histology was noted. Malone et al(1992) undertaking similar experiments found that ultrasound images taken immediately after ILP tended to overestimate the extent of necrosis and later images tended to underestimate the extent of necrosis. Bosman et al(1991) performed ILP in porcine liver and found good correlation of ultrasound findings and subsequent histology. There appears to be some disagreement then as to whether ultrasound can accurately predict the extent of laser damage. Ultrasound is however useful at allowing accurate placement of the laser fibre and possibly in giving an indication of the extent of the tumour.

4.8.3 Computerised Tomography(CT)

Only one study has compared CT findings with histology after ILP. Amin et al(1993b) performed ILP in 18 Wistar rats using the Nd-YAG laser. Pre-contrast, contrast enhanced dynamic and delayed CT's were performed before and after ILP. There was a good correlation between the necrosis size on CT and the subsequent histology and the optimal technique for matching the extent of necrosis was dynamic contrast enhanced scanning.

4.8.4 Magnetic Resonance Imaging(MRI)

In theory MRI should be superior to other imaging modalities as a method of predicting the extent of ILP induced necrosis because firstly MRI is sensitive to alterations in the dynamics of water-macromolecular interactions(Bottomley et al, 1984), therefore any change in the state of tissue water should be visible on MRI. Secondly, MRI can map tissue temperature changes(Jolesz et al, 1988).

Matsumoto et al(1992) studied ILP monitored by MRI in an ex-vivo liver model. They showed an increasing area of low signal density during ILP. The area regressed after ILP but did not correspond to the subsequent histological findings. A reversible signal loss has been reported by Higuchi et al(1992) when using T1 weighted standard spin echo sequences. Anzai et al(1992) found a high signal intensity rim which corresponded to an area of oedema which progressed to necrosis by 7 days after ILP. Tracz et al(1993) induced ILP in the brain of cats and monitored the changes using proton spin echo MR images during and immediately after ILP and at 2,5 and 14 days. An enhancing halo on contrast enhanced T1 weighted images acquired immediately after ILP best approximated the necrotic lesion diameter at 2 days. T2 weighted images acquired during and immediately after ILP consistently underestimated the total lesion diameter at 2 days. These studies have demonstrated that MRI has considerable promise in delineating the full extent of laser damage but more work is needed to optimise the sequences.

4.8.5 Invasive monitoring techniques

If non invasive imaging techniques are not forthcoming then invasive probes measuring blood flow, light distribution or temperature may be beneficial. Daikuzono et al(1988) reported the use of a computer controlled Nd:YAG system to produce ILP.Temperature sensors were placed directly into the target organ. If the temperature at the sensing probes dropped below or rose above a certain set limit the laser output would be adjusted accordingly maintaining a steady temperature in the tissue with a high degree of accuracy. Thermocouples can be used to monitor tissue temperatures during ILP but have the disadvantage of being invasive and in addition they only give a point temperature measurement which is unsatisfactory because tumours have a non-uniform heat distribution(Fessenden et al, 1984). Invasive probes measuring blood flow are not a reliable predictor of the extent of necrosis(Masters, 1993)

4.9 ILP Clinical

4.9.1 Clinical work in liver metastases

Hepatic metastases from colo-rectal cancer present a major clinical problem worldwide. Current treatment options for patients with hepatic metastases include resection(but only 5-10% are thought suitable for this procedure), systemic chemotherapy, regional hepatic artery perfusion, hepatic artery embolization or external radiotherapy. Resection improves survival from virtually zero without treatment to 23-49% after surgery(Amin et al,1993) and is the only treatment modality currently of proven benefit. However the procedure does carry a significant morbidity of 12-25% and a mortality rate of 4-12%(Masters et al, 1991). There is a place then for a minimally invasive procedure which could destroy metastases without the morbidity or mortality associated with surgery. Various treatments have been tried including radiofrequency electrocautery, cryosurgery, percutaneous alcohol injections, interstitial radiotherapy and focused ultrasound. Each of these modalities have their advantages and disadvantages and are discussed in detail elsewhere(Amin et al, 1993c and Masters et al, 1991).

Interstitial laser photocoagulation as a treatment modality for the local destruction of liver metastases was first used clinically by Hashimoto et al in 1985. A modified diffuser tip was inserted into metastases at laparotomy and the tumours treated with 1000 Joules from a Nd-YAG laser. Steger et al(1989) were the first to describe percutaneous ILP of liver metastases under ultrasound guidance. Two patients were described, both with hepatic metastases from colo-rectal carcinoma. Treatment took place under local anaesthesia, sedation and analgesia with antibiotic cover. Tumour necrosis was evident on ultrasound in both patients and on follow up CT scanning in one patient. The first patient was treated with a single fibre and four sites were treated. The second patient was treated with the four fibre system using the beam splitter. Both patients tolerated the procedure well and no complications were reported. Amin et al(1993) recently reported an update of the National Medical Laser Centre experience of treating liver metastases with ILP. They described treatment of 27 patients with a total of 74 liver metastases. Median tumour size was 2.5 cms(range 1-15cm) and the median number of tumours per patient was 3(range 1-10). Nineteen patients received some form of chemotherapy in addition to ILP. All patients underwent ILP under local anaesthesia, sedation and antibiotic cover. ILP was performed using the Nd-YAG laser and the four fibre system. The laser was set at a power of 2 Watts per fibre for 500 seconds. Ultrasound was used to allow correct positioning of the fibres within the tumour and to monitor thermal changes during ILP. Following initial treatment the fibre tips were carefully re-positioned(in some patients with larger tumours) by withdrawing them approximately 1.5 cms and the treatment repeated. Each patient had between one and eight treatment sessions and the total energy used ranged from 5,000 to 34,000 Joules. Dynamic CT scans were performed before and within 24-72 hours after ILP and laser induced necrosis assessed by comparing pre and post treatment contrast enhanced CT scans. ILP necrosis was noted as an area of non-enhancement on the post treatment dynamic CT scan. Tumour necrosis was divided into three categories by Amin et al(1993): Grade I(100% necrosis), Grade II(50-99% necrosis) and GradeIII(<50% necrosis).

Amin et al(1993d) described an expanding hyperechoic zones around each fibre tip seen on ultrasound scanning during ILP(similar to those described by Steger et al, 1992) and the echogenic zone was able to predict the extent of necrosis well(as measured on subsequent CT scans) for small tumours 2cm or less in diameter but not for larger tumours. Following ILP it was difficult to differentiate treated areas within the tumour from viable untreated tumour tissue. All of the tumours treated showed some evidence of necrosis on follow up dynamic CT scanning and 63% of patients had a reduction in their total tumour volume of greater than 50%. A Grade I necrosis occured in 55% of tumours, a Grade II necrosis in 31% and a Grade III in 14%. Tumours which showed 100% necrosis(i.e. a Grade I necrosis) were smaller than those with a Grade III necrosis(median 2 vs 5.5 cms) and required fewer treatments(median 1 vs 2.5 sessions). Few complications were reported and all patients were discharged at 24 hours post ILP. Amin et al(1993c) using a Kaplan Meier life table analysis were able to give an estimated 1 year survival of 84% and a 2 year survival of 74%. Analysis of the survival data should be made with caution as the study consisted of small numbers of patients and the follow up is short. More patients and ultimately a controlled clinical trial will be required to assess its efficacy. However, the study has shown that ILP can induce significant necrosis in liver metastases with few complications under sedation and local anaesthesia/analgesia and a minimal hospital stay.

4.9.2 Clinical work in pancreas and prostate

Carcinoma of the pancreas is the fourth commonest cause of cancer related death in the United Kingdom and accounts for 6,000 deaths every year. The incidence of the disease has trebled in the last 50 years and the overall 5 year survival is less than 5%(Masters and Bown,1990a). Masters and Bown(1990b) described 3 patients who had inoperable recurrent pancreatic cancer treated with ILP. Tumour necrosis was evident on subsequent post ILP CT scans in all 3 patients. All 3 patients died of their disease(mean survival was 7 months) and post mortem analysis in one patient showed well defined areas of cystic tumour necrosis 6 weeks after the last laser treatment(Masters and Bown, 1990b).

Amin et al(1993e) described the use of ILP in a 65 year old patient with recurrent prostatic carcinoma following radical radiotherapy to the prostate. Three 18G needles were inserted into the prostate transperineally and fibre tip positioning was achieved with the use of transrectal ultrasound and CT scanning. ILP was performed using a diode laser under local anaesthesia and a total of 3000 Joules delivered to the tumour. Clear evidence of necrosis was evident on follow up CT scanning 10 days after ILP and subsequent biopsies from the area confirmed the presence of necrosis. The patient tolerated the procedure well and no complications arose.

4.9.3 Clinical work in breast cancer

Steger et al(1989) were the first group to describe the use of ILP in a patient with breast cancer who refused all forms of conventional treatment, including surgery, radiotherapy or tamoxifen over a two year period. The tumour volume was calculated with ultrasound. Three tumour sites were treated with ILP under local anaesthesia and subsequent follow up ultrasounds were said to show a reduction in tumour volume although no correlation with histology was possible. Masters and Bown(1990b) subsequently described ILP in a further three patients, two of whom underwent surgery. Following surgery(several hours to 5 days after ILP) small but definite areas of necrosis were evident within the tumours. The treatment was not associated with any adverse side effects. The safety and the observation that necrosis can be produced in breast cancers following ILP have encouraged further studies into the potential value of ILP as a means of *in situ* percutaneous destruction of breast cancers, the work of which forms the basis for this thesis.

4.10 Summary

Interstitial laser photocoagulation was first described by Bown in 1983 and involves insertion of a laser fibre(or fibres) directly into the target organ. The laser is activated at low powers using long exposures resulting in predictable areas of necrosis. Experimental work suggests that necrotic areas of up to 16 mm can be produced using a

single fibre and up to 40mm using 4 fibres fired simultaneously. The areas healed safely by means of resorption and fibrosis. The 1064nm Nd-YAG laser was thought of as being the best laser for ILP but the 1320nm Nd-YAG and the diode laser appear to produce larger necrotic lesions using a clean fibre. The presence of charring is associated with larger diameters of necrosis, the laser fibre tip acting as a point heat source and pre-charring the fibre may be of value in increasing necrotic diameter when using the Nd-YAG laser at 1064nm. ILP has little potential as a clinical tool for *in situ* tumour destruction unless some form of imaging device is available which will accurately map out the boundaries of the tumour and accurately predict the final extent of necrosis. Ultrasound has been investigated with discordant results, MRI and CT appear more promising.

ILP has been described clinically in the treatment of liver metastases, pancreatic, prostate and breast cancers and clear evidence of tumour necrosis with few complications have been described. Whether this will translate into an improvement in overall survival for hepatic, pancreatic and prostate cancers awaits the results of larger studies and eventually randomised clinical trials.

CHAPTER 5 : A SURVEY OF THE MANAGEMENT OF BREAST CANCER IN ENGLAND AND WALES

5.1 : Introduction

The main purpose of this thesis is to investigate the potential use of a new minimally invasive technique for *in-situ* breast tumour ablation. As part of the background work we decided to undertake a survey of surgeons to see what place conservative surgery has in the day to day management of patients with early breast cancer.

Breast cancer is, in this country, the most common cancer affecting females with 26,000 new cases and 15,000 deaths per year . The United Kingdom possesses the unenviable record of not only having one of the highest incidence of the disease but also the highest death rate in the world(Chamberlain, 1989). Despite this, few guide-lines exist for the management of symptomatic breast cancer and those that have been set out, for example by the Kings Fund, are not followed in clinical practice(McCarthy and Bore,1991, Chouillet et al, 1994). The management of the disease does seem to affect survival ; in a recent publication Basnett et al(1992) have shown a survival advantage for patients treated in a teaching rather than a non teaching hospital although this difference was probably attributable to the more liberal use of chemotherapy at the teaching centre.

The surgical management of the primary tumour has changed dramatically in recent years. With the publication of the results of prospective trials with strong statistical correlation comparing conservative surgery, axillary clearance and radiotherapy with mastectomy and axillary clearance, Veronesi et al (1981) and Fisher et al(1985) among others have been able to show that conservative surgery and radiotherapy have equal results in terms of local control and overall survival to that of mastectomy in selected patients. The publication of these results caused a change in the surgical management of breast cancer in this country. In 1984, Gazet et al(1985) showed that 84% of surgeons in England and Wales regularly performed mastectomy. In 1987 Morris et al(1989) found that 43% of English surgeons would undertake mastectomy for a T_1 tumour and in a follow up study in 1991(Morris et al, 1992) only 13% of surgeons performed a mastectomy for a similar tumour. Whilst an increasing number of surgeons perform

breast conserving surgery rather than mastectomy one of the major areas of controversy and disagreement surrounds the surgical management of the axilla. Disagreement also exists about many aspects of the management of breast cancer partly due to lack of clinical trials and partly due to differing interpretations of existing data.

5.2 Aims of the study

The purpose of this study was to obtain an overview of the way surgeons in England and Wales are investigating, treating and following up patients with breast cancer in 1992-3 and to assess trends in management by comparisons with previous surveys.

5.3 Materials and Methods

The names of all consultant general surgeons in England and Wales were obtained from the Medical Directory(1992). A questionnaire was sent to each surgeon by post and a stamped addressed envelope included in anticipation of a reply. The questionnaire was sent to 985 consultant surgeons. The questionnaires were sent out during the period August-December 1992. The replies were analysed using a Paradox® relational database programme(Borland International Ltd).

The surgeons were asked the following questions:--

1.The number of surgeons dealing with breast cancer in their particular hospital.

2.The methods used to obtain a tissue diagnosis from a patient who presented with a hard lump in the breast.

3.The surgical management of a carcinoma in the upper outer quadrant of a patient with a large breast and a 2cm tumour(for pre and post menopausal patients)

4. The management of the axilla(for pre and post menopausal patients)

5.The management of an otherwise fit 82 year old patient with a breast carcinoma.

6. The management of a 62 year old patient who presents with a recurrence of her carcinoma following treatment by segmental mastectomy, radiotherapy and adjuvant tamoxifen.

7.The subsequent management of a 45 year old patient with a 2cm carcinoma treated by segmental mastectomy whose histology showed tumour present at the resection margins.

8.Whether the surgeon considered follow up of their breast cancer patients worthwhile.

9.The length of follow up of breast cancer patients.

10.Whether the surgeon performed regular follow up investigations on their breast cancer patients(e.g.bone scans) if the patient remained asymptomatic

11.The frequency that the surgeon would perform mammography following conservative surgery and radiotherapy for breast cancer. A copy of the questionnaire is included in the appendix.

5.4 Results

By the end of February 1993, 599 replies were received, a response rate of 61%. 132 surgeons indicated that they did no breast surgery, one surgeon wrote to say that he was unable to fill in the questionnaire and one refused to complete the form, leaving 465 completed questionnaires for analysis.

Initially the surgeons were asked how the workload of breast cancer was distributed in their particular hospital. One hundred and fourteen surgeons(25%) indicated that breast cancer was largely managed by one consultant whilst 344(74%) indicated it was managed by more than one consultant and 7(1%) did not reply.

Methods used to obtain a tissue diagnosis

Three hundred and ninety five surgeons(85%) indicated that they would use fine needle aspiration cytology to obtain a tissue diagnosis from a patient who presented with a hard lump in the breast, 32(7%) indicated that they would perform an excision biopsy, 26(5.5%) indicated that they would perform a core biopsy and 12(2.5%) would perform either a core biopsy or undertake an excision biopsy.

Treatment of the primary tumour

Three hundred and sixty five(79%) surgeons indicated that they would recommend conservative surgery(either tumourectomy or segmental mastectomy) for a pre-menopausal patient with a 2cm carcinoma in the upper outer quadrant of a large breast. Thirty(6%) would recommend mastectomy and 70(15%) would offer the patient the choice of mastectomy or conservative surgery. For a post-menopausal patient with a similar tumour, 367(79%) recommended conservative surgery, 31(7%) mastectomy and 67(14%) the choice of breast conservation or mastectomy.

Geographical variations in the management of the primary tumour.

The response rate varied by region from 38% (Mersey) to 75% (London Special area health authority).The number of surgeons completing the questionnaire, the number recommending mastectomy, and the regions are outlined in table 5.1.

Region	No. surgeons completing survey	No. surgeons recommending mastectomy	Percentage
North	89	5	5.6 %
Central	100	8	8 %
South	220	5	2.3 %

Table 5.1:Surgeons preferences to treat a pre-menopausal patient with a T_1 breast carcinoma by region.

Therefore in this study only 18 surgeons in England would recommend mastectomy as an initial treatment. Twenty eight percent of the surgeons who would recommend mastectomy came from the North, 44 % came from the Central areas and 28% came from the South. In this study there was a trend toward mastectomy being recommended more frequently in the central areas rather than in the North or South, however this difference failed to achieve statistical significance (p=0.06).

The treatment of the axilla

Regarding the treatment of the axilla for a pre-menopausal patient with a 2cm. tumour in the upper outer quadrant, 196(42%) would undertake a full axillary dissection and 171(37%) axillary sampling. Twenty eight(6%) would perform a full dissection only if the axillary nodes were palpable, 20(4%) would normally only perform axillary sampling but would perform an axillary dissection if the nodes were palpable, 17(4%) would normally only perform axillary sampling if axillary nodes were palpable, 14(3%) would leave the axilla alone and 17(4%) either did not reply or gave an answer not listed in the choices.

For a post-menopausal patient with a similar tumour 145(31%) indicated that they would perform a full axillary dissection and 164(35%) axillary sampling. Thirty seven(8%) would perform axillary sampling in the presence of gross axillary disease, 35(7.5%) a full dissection in the presence of palpable axillary disease, 23(5%) would normally perform axillary sampling but would perform a full axillary dissection in the presence of palpable axillary disease, 33(7%) would leave the axilla alone and 28(6%) either did not reply or gave an alternative answer not listed in the choices.

Breast cancer in elderly women

One hundred and seventy three surgeons(37%) indicated a preference to treat an otherwise fit 82 year old lady with breast cancer by lumpectomy and tamoxifen whilst 162(35%) would recommend tamoxifen alone, 25(5%) advised simple mastectomy, 18(4%) lumpectomy and radiotherapy and 76(17%) gave a miscellaneous group of answers that included lumpectomy or mastectomy with or without tamoxifen, lumpectomy or mastectomy with or without radiotherapy. Eleven surgeons(2%) did not reply.

The treatment of local recurrence

The majority of surgeons(320 or 69%) would treat a local recurrence following lumpectomy, radiotherapy and tamoxifen by mastectomy, 27(6%) would perform a further excision of the area, 26(6%) would recommend either mastectomy or would try another endocrine preparation such as medoxyprogesterone acetate. Seventeen(4%) would recommend mastectomy or chemotherapy, 13(3%) mastectomy or further excision of the tumour , 12(3%) further excision or another endocrine preparation, 13(3%) would try another endocrine preparation, 7(2%) would recommend chemotherapy and 22(4%) either did not reply or gave another answer not listed in the choices.

Incomplete excision

One hundred and seventy five surgeons(38%) indicated that they would perform a mastectomy if, following segmental mastectomy of a 2cm cancer, the histology report subsequently showed tumour present at the resection margins. Seventy nine(17%) would perform a further excision, 75(16%) would recommend either further surgery(mastectomy or further excision) or would refer for radiotherapy, 41(9%) would give the patient the choice of either further excision or mastectomy, 41(9%) would refer for radiotherapy, 9(2%) would either refer for radiotherapy or suggest giving chemotherapy, 6(1%) would prescribe chemotherapy, 24(5%) gave an answer not listed in the choices and 16(3%) did not reply.

Follow up of breast cancer patients.

When the surgeons were asked if they considered follow up of breast cancer patients worthwhile, 420(90%) indicated that they did and 38(8%) indicated that they did not and 7(2%) did not reply. One hundred and thirty seven(29%) would follow their patients up for 1-5 years, 124(27%) for 5-10 years, 152(33%) for greater than 10 years or for life and seven(1%) did not reply.

Follow up investigations

Three hundred and nineteen(69%) surgeons did no follow up investigations such as bone scans and routine chest X-rays(excluding mammography) on asymptomatic patients, 134(29%) indicated that they did and 12(2%) did not reply.

Following conservative treatment with lumpectomy and radiotherapy surgeons indicated that they would perform follow up mammograms, 134(29%) every 2 years, 115(25%) annually, 46(10%) every three years, 15(3%) at 1 year then on alternate years, 13(3%) every 2-3 years, 41(9%) would not routinely perform follow up mammography, 72(15%) gave miscellaneous replies and 29(6%) did not reply.

5.5 Discussion

In terms of the actual number of replies, this study is the largest audit of the surgical management of breast cancer that has been undertaken in this country. The major areas which require discussion concern changes in the surgical management of the disease which have occurred and discussion concerning consensus and lack of consensus in patient management.

Several changes have occurred in breast cancer management when comparisons are made with previous surveys. Fine needle aspiration(FNAC) cytology appears to have largely superceded excision biopsy as a means of obtaining a tissue diagnosis and is now practised by the majority of surgeons in England and Wales. Only 7% of surgeons would now routinely admit their patients for an excision biopsy and many of them indicated that they did not have cytology facilities but would like to use FNAC if it were available. Lack of these facilities inevitably commits many patients to unnecessary surgery and in some cases to more than one surgical procedure which has obvious financial implications. Although no previous surveys have nationally audited the increase in the use of cytology as opposed to excision biopsy a study by Basnett et al(1992) comparing breast cancer management at a teaching and non-teaching hospital did demonstrate an increasing trend toward the use of cytology as opposed to core biopsy or excision biopsy as a means of obtaining a tissue diagnosis over the five year period 1982-86.

We have also been able to demonstrate a further swing in the use of conservation surgery as opposed to mastectomy in the treatment of early breast cancer. It should be pointed out that the question referred to a specific clinical setting(i.e. a 2cm carcinoma in the upper outer quadrant of a large breast) and was deliberately meant to be similar to the question posed by Morris et al in their survey's of 1987 and 1991 and does not mean that only a small number of surgeons would undertake a mastecomy for a patient with a 4cm central carcinoma in a small breast, for example. Nevertheless there has been an enormous change in the surgical management of the tumour with 43% of

surgeons undertaking mastectomy for a T1 tumour in 1987(Morris et al, 1989) this figure has steadily fallen to 6% in 1993. Presumably this change in management has occurred following the publication of the results of several large randomised prospective trials(Veronesi et al, 1981, Fisher et al, 1985) demonstrating the safety of conservation surgery when combined with radiotherapy and thence compared with mastectomy(for selected patients) and as a result of patient preference and public awareness of these results. There was no difference in surgeons treatment preferences when presented with a pre or post-menopausal patient with breast cancer.

The axilla is possibly the area of greatest controversy in the surgical management of breast cancer(Fentiman and Mansel, 1991, O'Dwyer, 1991). More surgeons appear to be undertaking axillary surgery in combination with conservative surgery than they did in the past. Gazet et al(1985) found that only 16% of surgeons performing conservative surgery would biopsy ipsilateral axillary nodes in 1983 but by 1987(Morris et al,1989) 61% did so (although only 44% would perform a full axillary clearance) and now we have found that 83% of surgeons would biopsy the ipsilateral axilla routinely with a further 10% undertaking axillary dissection if there was palpable axillary disease for a pre-menopausal patient. Axillary surgery in post-menopausal patients was undertaken routinely by 71% of surgeons with a further 15% undertaking axillary surgery for palpable disease. The axilla was not explored by 3% of surgeons for pre-menopausal and 7% for post-menopausal patients. The findings of the recent overview(Early breast cancer trialists collaborative group, 1992) and other studies on the use of adjuvant chemo-endocrine therapy suggesting a significant survival benefit for pre-menopausal node positive patients receiving chemotherapy may account for the increasing "popularity" of axillary surgery.

Although many surgeons have indicated that they would biopsy the axilla the surgical world is divided as to the exact procedure that should be performed. Some authorities suggest that full dissection of the axilla not only provides valuable prognostic information but is also an effective way of controlling disease locally(Veronesi et al,

1990) whilst others (Steele et al, 1985) have been able to show that axillary sampling provides sufficient information to plan appropriate adjuvant therapy. The number of surgeons who would advocate full axillary dissection does not appear to have altered, 44% in 1987 and 42% for pre and 31% for post-menopausal patients in this study. Arguments for and against both techniques and arguments against axillary surgery of any sort can be found elsewhere(See chapter 2 and Sacks et al, 1992).

Breast cancer in the elderly has been treated by tamoxifen alone following reports from uncontrolled trials suggesting that endocrine treatment could be used alone as an effective treatment(Preece et al, 1982). However, the results of the Cancer Research Campaign(C.R.C.) trial(Bates et al, 1991) comparing tamoxifen with tamoxifen and surgery in elderly women have shown a survival disadvantage for patients treated by tamoxifen alone when compared to tamoxifen and surgery. A more detailed analysis of the data revealed that the local recurrence rate was five times higher in those patients treated by lumpectomy and tamoxifen rather than mastectomy and tamoxifen suggesting that breast cancer in the elderly should be treated in the same way as in younger women. It is interesting to see that the number of surgeons who advocate surgery and tamoxifen is approximately equal to the number advocating tamoxifen alone but the number who would advocate mastectomy, which is probably the best way of treating an elderly patient with breast cancer, was only advocated by 5% of surgeons. Whether the number advocating endocrine treatment alone decreases as a result of the publication of studies like the C.R.C. study and other review articles suggesting the superiority of surgery and tamoxifen(Dixon, 1992) remains to be seen, but clearly the results of studies like the C.R.C. study have not yet been translated into everyday clinical practice. There are no previous studies looking at the way surgeons treat breast cancer in elderly women and so an analysis to assess management trends is not possible.

Local recurrence following breast conserving surgery and radiotherapy is said to occur in around 8% of cases by 5 years(Fisher et al, 1985), although much higher recurrence rates have been reported(Locker et al, 1989). The majority of surgeons(69%)

participating in this study would perform a mastectomy for local recurrence with only 6% performing a further excision of the recurrence. Mastectomy appears to offer the best chance of achieving local control in this situation rather than further local excision which was advocated by 6% although there was a wide variety of different management options.

Incomplete excision of a breast cancer has been implicated in a higher incidence of local recurrence in several studies(See Chapter 2.1.3c). It is interesting to note that 38% of surgeons would proceed to mastectomy on the basis of the histological results showing tumour present at the resection margins with only 17% performing a further wide excision of the area. The published data on local recurrence and resection margins are all retrospective involving a wide variety of patients, the definition of what constitutes a positive margin varies from one study to the next and although there is a suggestion that the local recurrence rate is higher if the margins are involved this has not been proven prospectively. Again this study has shown a great variation in treatment methods for this particular problem.

Follow up of breast cancer is thought to be worthwhile by 90% of surgeons although many commented that they thought that the major value of following up breast cancer patients was for the psychological benefit of the patients rather than for oncological reasons. The value of follow up has been questioned, seemingly the detection of metastases is low considering the number of patients who are reviewed and it appears from other studies that when patients do develop a recurrence, be it local or distant, they do so in the interval between clinic visits(Morris et al, 1992).

There is very little evidence that detection of metastases at an early stage and thence early treatment alters prognosis. In a trial by Zwaveling et al(1987) they were unable to detect a survival advantage for treating asymptomatic breast cancer metastases. Although there is no evidence to suggest a survival advantage for follow up of breast cancer patients nevertheless the vast majority of surgeons do follow up their patients on

a regular basis but there appears also to be little consensus as to how long these patients should be followed up, with approximately a third following their patients for up to five years, a third following them up for 5-10 years and the final third following them up for 10 years or for life. The majority of distant metastases occur in the first five years although 17% of breast cancer patients die between five and ten years after diagnosis(Young, 1989), there appears to be some rationale then to follow up patients up to ten years. If surgeons are to follow up breast cancer patients perhaps guidelines should be introduced to lay down the optimal timing of follow up.

Twenty nine percent of surgeons regularly did follow up investigations on their breast cancer patients even if they remained asymptomatic. In a study by Rutgers et al(1989) 416 patients were followed up for a mean of 5 years. Patients were followed up by clinical examination, regular radiographs and blood screens.Of 8005 radiographs only 24(0.3%) revealed asymptomatic metastases and of 17,000 blood tests only 10 revealed asymptomatic metastases(0.05%). As metastatic breast cancer is essentially incurable and no survival advantage has been demonstrated for treating asymptomatic metastases the necessity to pick up early asymptomatic metastases seems futile, resulting in a large number of negative investigations and an unnecessary drain on financial resources.(e.g.a bone scan privately costs £170, a chest X-ray £50 and a liver ultrasound, £155). Regular mammography has the advantage of detecting local recurrence after breast conserving surgery and radiotherapy as well as detecting early metachronous disease.The advantage in detecting early local recurrence as opposed to early distant metastases, is that early treatment may offer the advantage of superior local disease control. In our study only 9% did not perform regular mammography. Among those surgeons who did perform regular mammography there seems to be little consensus as to the most appropriate time to perform it. This is probably because there are no studies outlining the optimal time interval at which mammography should be performed in this high risk group, and we would argue that a controlled trial be set up to find the optimal time interval for mammography in these high risk patients.

This study has shown that there is very little consensus on the management of breast cancer in this country. The only area where there was greater than 80% consensus on management was in the treatment of the primary tumour where most surgeons now agree that the primary tumour (in selected patients) can now safely be treated by local excision as opposed to mastectomy. It must be emphasised that the major reason that this consensus has arisen is because of the publication of the results of large prospective randomised clinical trials by such clinicians as Veronesi et al(1981) and Fisher et al(1985). In this study we can see that breast cancer is managed in most hospitals by more than one consultant and in another survey(unpublished data) we have shown that there is very little evidence that the management of breast cancer is in the hands of those with a special interest in the subject. We would advocate then that the management of patients with breast cancer should now be in the hands of those with a special interest in the subject. Such surgeons will be more aware of current literature and ongoing clinical trials, more patients will then be entered into existing clinical trials(currently only 7% of patients are entered into clinical trials: D.Riley, personal communication) and further trials set up to sort out the areas where there is disagreement in management. If these criteria are met then a similar survey ten years hence will show a greater consensus about management and possibly an improvement in the death rate of breast cancer in the United Kingdom such that it is more in line with other westernised countries.

CHAPTER 6: INTERSTITIAL LASER PHOTOCOAGULATION FOR BREAST CANCER: QUANTITATIVE STUDIES

6.1 Introduction

The work included in this thesis so far has shown how the treatment of breast cancer has essentially done an about turn in the last one hundred years. Moving away from conservative treatment toward more radical surgery and then more recently toward conservative surgery again. The overview of trials(chapter 2)comparing conservative surgery and mastectomy has illustrated the efficacy and safety of conservative surgery for selected patients. The work published in chapter 5 has shown how these trials have translated into a significant change in the way surgeons in the United Kingdom treat patients with early breast cancer with a swing away from mastectomy toward conservative surgery. In 1987 40% of surgeons(Morris et al, 1987) indicated a preference to treat a patient with a T_1 carcinoma by mastectomy and this figure has now fallen to 6%. The work presented in chapter 4 has outlined the basic principles of interstitial laser photocoagulation(ILP) and shown how the early work in both experimental animal models and in treating hepatic metastases in the clinical setting has shown that ILP is safe and capable of inducing predictable amounts of necrosis *in situ* with few complications. However, the technique would have little value for *in-situ* tissue destruction unless it can be performed in conjunction with an imaging technique that will accurately predict the full extent of laser damage. The work reviewed in chapter one and four has outlined the progress being made, not only in the imaging of breast cancer, but also in the imaging of ILP.

Taking the concept of conservative surgery for breast cancer a step further the main thrust of this thesis is to ask whether it would be possible to destroy breast cancers where they arise using ILP and some form of imaging technique and leaving the area to heal via resorption and fibrosis.

6.2 Aims of the study

The aims of this study are:-

1. To study the biology of laser interactions with breast cancer. To assess how much necrosis could be produced using one laser fibre inserted directly into a breast cancer and the nature of subsequent healing and any complications.

2. To perform range finding experiments to optimise the laser parameters of power and exposure time.

3. To find an imaging technique that will allow (a) accurate placement of the laser fibre within the tumour (b) accurate assessment of the margins of the tumour (c) real time monitoring of hyperthermic changes and (d) accurate prediction of the final extent of thermal necrosis.

The aims of the study were to undertake ILP under local anaesthesia in the interval between diagnosis and surgery(surgery was not delayed because of the ILP). It was not intended to completely destroy the tumour but simply to assess how much damage could be obtained by inserting one laser fibre into the tumour at various powers and time exposures. During ILP various imaging techniques were employed to guide the laser fibre into the tumour and to monitor laser induced changes. The diameter of necrosis as measured on the imaging techniques were compared with the diameters of necrosis in the final resected specimen.

6.3 Materials and Methods

6.3.1 Patients

Forty five patients from University College Hospital and The Royal Surrey County Hospital were included in the study which began in January 1992. The diagnosis of breast cancer was made by fine needle aspiration cytology (or core biopsy) and mammography. No patients were entered into the study unless a definitive diagnosis of malignancy was made either by cytology or core biopsy even if the patient had clinical and mammographic evidence of malignancy. All patients entered into the study had a palpable carcinoma and, as the aims of the study were not to completely destroy the tumour, carcinomas of all sizes were accepted provided that they were to subsequently undergo surgery(i.e patients with impalpable carcinomas and advanced carcinomas to be treated by neo-adjuvant chemotherapy were excluded). All forty five patients underwent surgery and ILP was arranged in the interval between diagnosis and surgery. The interval between laser treatment and surgery was varied(the surgery was not delayed because of the study) to allow an accurate histological assessment of the way the tumour responded to the insult of the laser injury at different times after treatment.

Ethical approval for the study was obtained from the ethical commitees at both hospitals and informed consent was sought from all patients prior to the procedure.

6.3.2 Laser

A semiconductor laser was used (Diomed Ltd.®, Cambridge)which is easily portable (the size of a typewriter) and has a wavelength of 805nm which in the near infra-red spectrum has similar tissue penetration to the standard but less portable and larger Nd YAG laser with a wavelength of 1064 nm(Jacques et al, 1992). The laser is illustrated in figure 6.1. The diode laser has a power range of 0.5 to 25watts, is air cooled and requires standard "mains" electricity supply and is therefore ideal for low power thermal therapy. In the delivery of laser energy to the tumour a single, freshly cleaved, 400μm fused silica fibre with a hard polymer cladding was used with a bare tip(Surgimedics Ltd®.U.S.A.) The fibre was sterilised in glutaraldehyde.

6.3.3 Equipment necessary for the procedure

The other items of equipment necessary to perform the technique are illustrated in figure 6.2:-

(i) Local anaesthesia using 2% lignocaine, plain or with adrenaline(Phoenix Pharmaceuticals Ltd, Gloucester, England)

(ii) 10ml sterile syringe and 23G sterile needle

(iii) Two 14G sterile intravenous catheters(Viggo products ®, Heisingborg, Sweden) with the outer plastic sleeve and the cap removed.

(iv) Sterile gauze and a sterile dressing towel(Vernaid Ltd ®.)

(v) Sterile gloves(Regent ®Biogel)

(vi) Savalon® or another non alcoholic skin cleansing agent

(vii) Several Sterets®

(viii) Elastoplast dressing

(ix) Sterile tape(not shown)

(x) Laser safety glasses(Diomed®, Cambridge)-not shown.

As well as the above equipment some form of imaging technique would be required. In the majority of cases in this study ultrasound was used to correctly place the fibre within the tumour and monitor any hyperthermic changes which occur during ILP. The ultrasound machines used were the Toshiba ® SAL 38B machine with the 7.5 MHz breast probe at the Jarvis breast screening centre, Guildford(Shown in Figure 7.3 together with the diode laser) and the Aloka ® 650(Japan) machine and the 7.5 MHz breast probe at University College Hospital, London. Computerised Tomography scanning(CT) was undertaken using the Siemens® Somaton DR at the Middlesex Hospital, London and intravenous contrast enhanced scans were performed using 20-40 mls of intravenous iodonated contrast agent(Iohexol 350mg/ml). Magnetic Resonance Imaging(MRI) was performed using the General Electric® G. E. Signa 1.5 Tesla scanner and the General Electric® breast imaging package at St. Mary's Hospital, Paddington , London. The tumour was enhanced by the use of 15mls of intravenous Dimeglumine gadopentate(469 mg/ml; Magnevist® Schering AG pharmaceutical

division, Germany). All procedures were undertaken in a laser approved room complying with local laser safety regulations.

Figure 6.1: The Diomed® diode laser

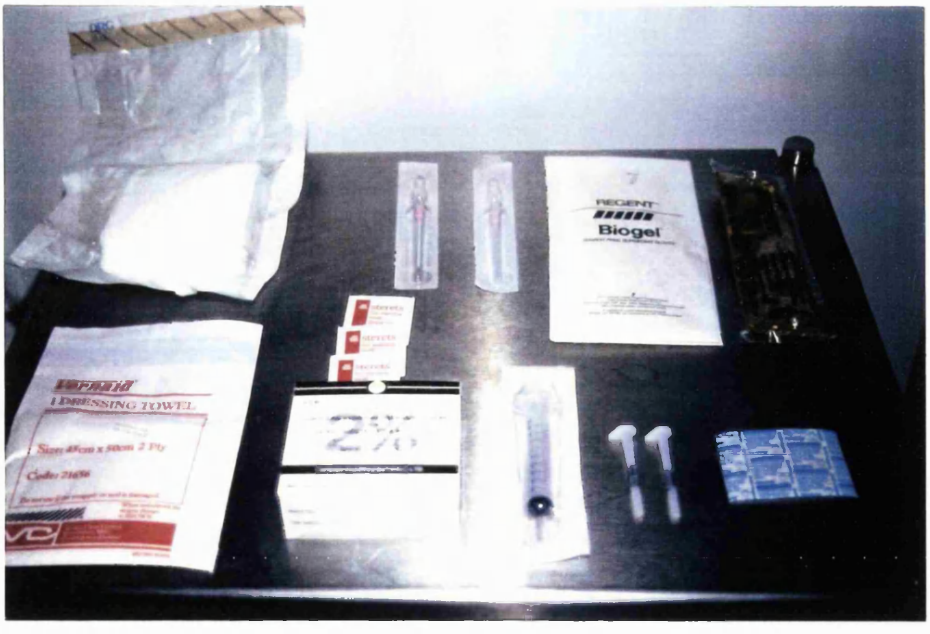


Figure 6.2: Equipment necessary for the procedure of ILP.

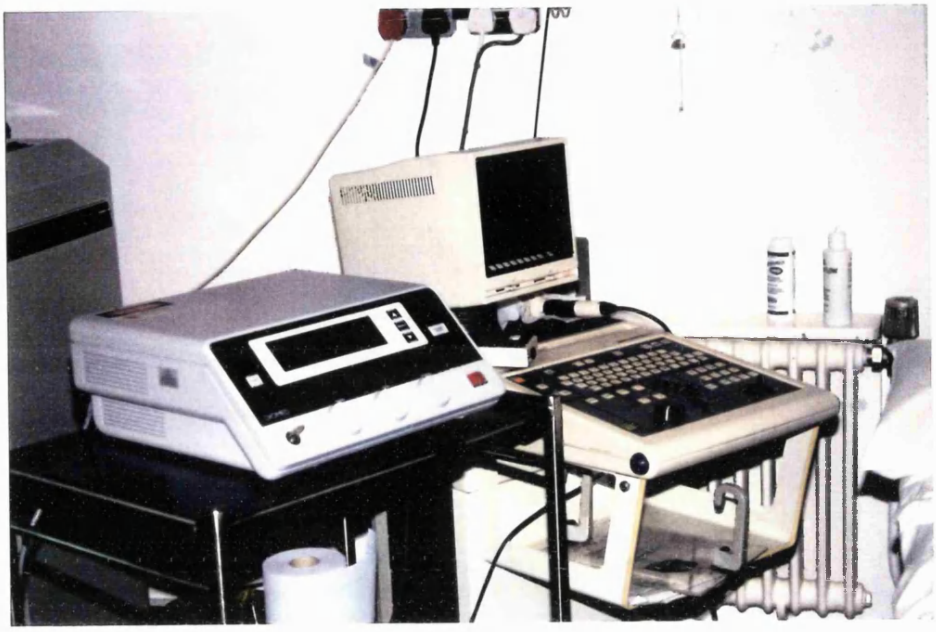


Figure 6.3: The Toshiba SAL 38B® ultrasound machine with the diode laser.

6.3.4 The Procedure

Under aseptic conditions the skin and the tissue surrounding the tumour were infiltrated with lignocaine 2%. Ultrasound was used to measure the dimensions of the tumour and the largest diameter was noted. Secondly, again under ultrasound control, the needle from a 14G cannula was inserted into the tumour and the position of the tip checked(Figure 6.4a) . Once a satisfactory position of the needle tip within the tumour was attained(defined as the needle tip present within the tumour on ultrasound) the laser fibre was advanced down the core of the needle to the tip and the needle withdrawn about 5mm so that the tip of the laser fibre lay bare within the tumour. The tumour was then treated with low power laser therapy(figure 6.4b and 6.5) with powers ranging from 2-3 watts and exposures of between 500-750 seconds in order to assess which laser parameters will produce the maximum necrotic diameter in the minimum time without complications(e.g. cavitation around the fibre tip). The changes to the tumour were monitored in real time by either ultrasound or CT scanning. The Ultrasound scanning was performed by three experienced radiologists (Dr. W.R. Lees, consultant radiologist and Dr. Zahir Amin, research fellow in radiology, The Middlesex Hospital, London and Dr. Julie Cooke, consultant radiologist, Royal Surrey County Hospital and Jarvis Breast Screening Centre, Guildford, Surrey) and by myself. The maximum diameter of hyperthermic changes seen on ultrasound was measured(figure 6.6 a and b) together with the maximum diameter of the tumour and following surgery the ultrasound images were correlated with the microscopic size of the tumour and the diameter of the laser induced damage. The measurement of the maximum size of the tumour and the maximum diameter of necrosis were not necessarily in the same plane and no attempt was made to cut the tumour in the same plane as the ultrasound.

CT scanning in real time was undertaken in 2 patients(The position of the needle and hence the laser fibre was checked under CT guidance). Once a satisfactory position of the needle was attained within the tumour the needle was again withdrawn about 5mm so that the tip of the laser fibre lay bare within the tumour. The laser was then activated. Intravenous iodonated contrast agent was given 2 mins after starting the laser, followed

by a 2-3 minute delay to allow the contrast to circulate and then scanning undertaken during the latter half of treatment, being completed at the same time as the laser treatment. Further CT scanning was then performed within the 5 minutes following the completion of treatment with the needle and fibre removed). Two other patients had dynamic enhanced CT scans prior to and 24 hrs following ILP and 2 further patients had dynamic enhanced CT scans 24 hrs after treatment. These latter four patients had ultrasound monitoring at the time of treatment. The hyperthermic changes that occurred either during or following ILP were seen as an area of reduced enhancement during dynamic CT scanning and the diameter of reduced enhancement was measured and again compared with the final diameter of necrosis in the resected specimen. Magnetic Resonance Imaging(MRI) using a contrast agent was performed in 5 patients before and within 24 hours of ILP treatment using T_1 weighted images. The laser induced necrosis was noted as an area of reduced enhancement following administration of intravenous contrast agent in the 24 hr post ILP scans.

Once the treatment was completed the fibre and needle were removed and the patient allowed home to be admitted at a later date for surgery. Surgery was performed by one of three surgeons(Mr.J.H.Scurr, consultant surgeon, University College Hospital, Mr.M.W.Kissin, consultant surgeon, The Royal Surrey County Hospital, Guildford, Surrey and myself at both hospitals) and consisted of either wide local excision with or without axillary clearance or modified radical mastectomy. Once the specimen had been removed it was incised immediately in the long axis of the tumour, the presence or absence of charring noted and the maximum diameter of the tumour and of the laser damage measured. No attempt was made to cut the tumour along the line of the fibre insertion or the plane of any of the ultrasound scans. The specimens were then fixed and underwent sectioning, staining with Haematoxylin and Eosin and histological examination by an experienced breast pathologist (Dr. M.E.F. Smith, senior lecturer in histopathology, University College London Medical School, London and Dr. M.G.Cook, consultant pathologist, The Royal Surrey County Hospital, Guildford, Surrey). The maximum diameter of laser induced damage was measured

microscopically and the specimen examined to assess the damage that the laser had caused both to the tumour and to surrounding normal breast tissue. The presence of any acute inflammatory reaction in response to the laser induced injury and evidence of healing were also noted.

It became evident early on in this study that larger diameters of necrosis were present when charring was noted in the tumour after ILP. We then undertook a study to see if by pre-charring the fibre(by placing a small drop of the patients blood on the end of the laser fibre and firing the laser at 10 watts for 2-3 seconds until a plume of smoke was evident) a larger diameter of necrosis could be obtained.

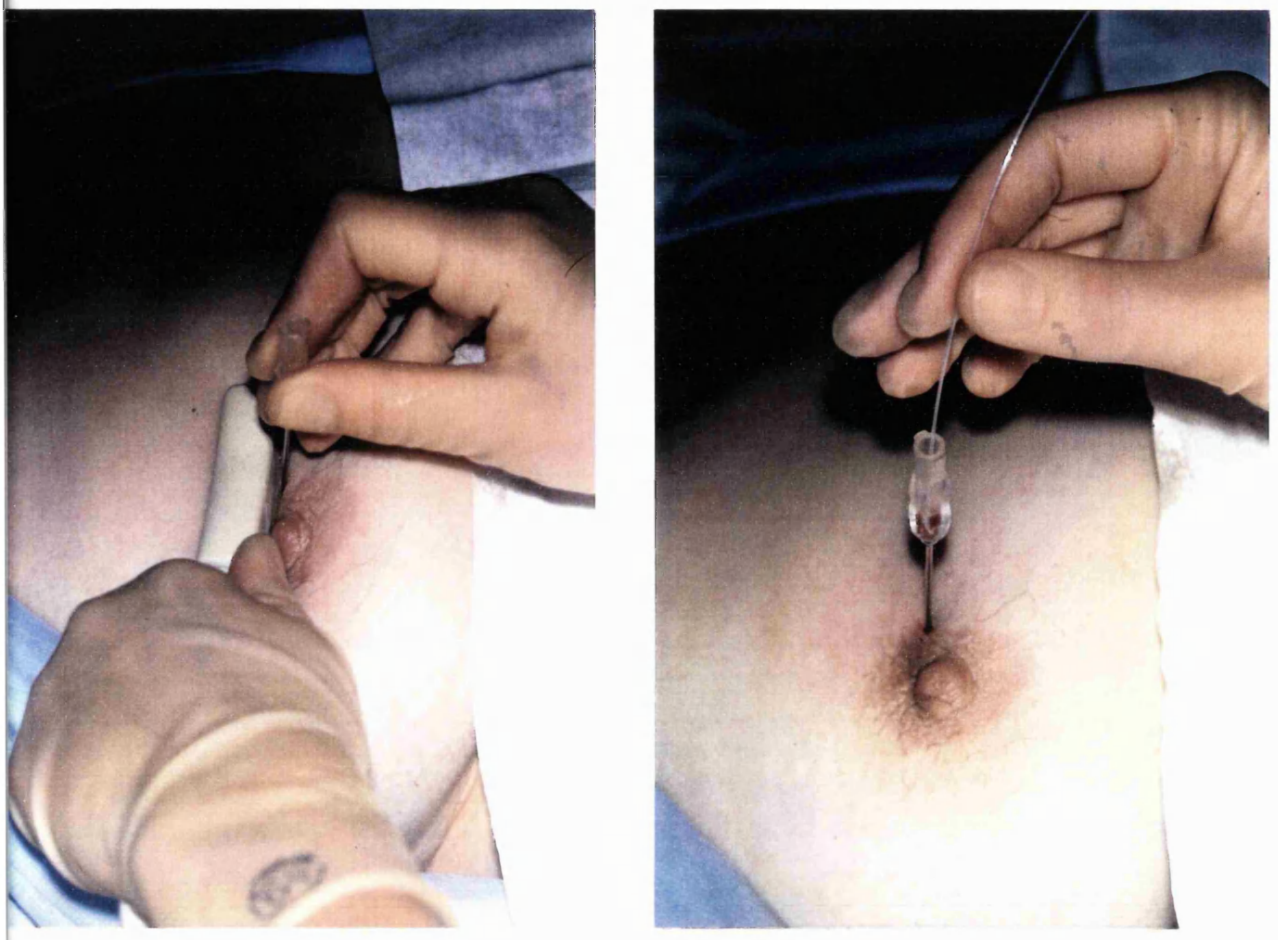


Figure 6.4: a) 14G needle inserted into the tumour under ultrasound control using the 7.5 MHz transducer and b) patient undergoing ILP.

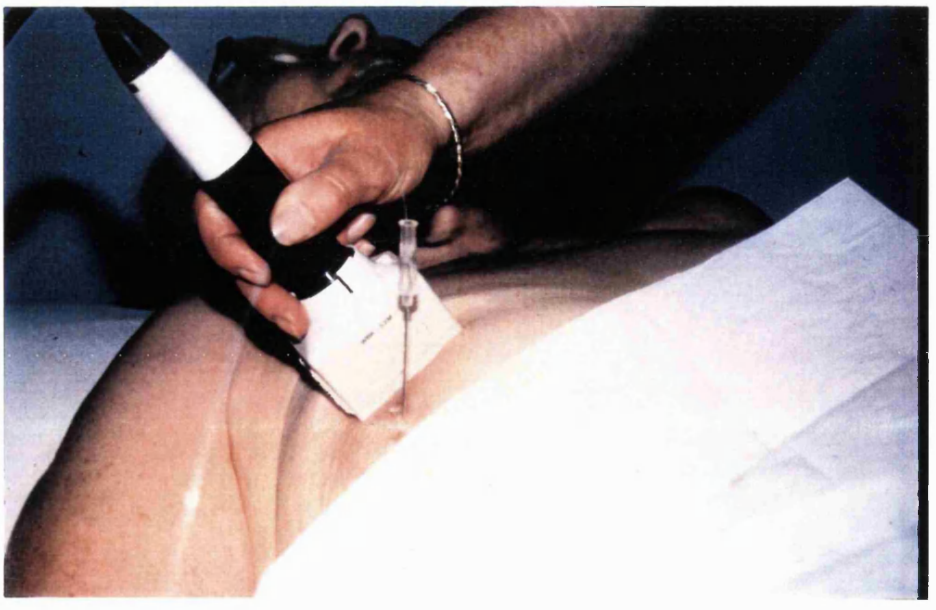


Figure 6.5: ILP in process using ultrasound to monitor hyperthermic changes.

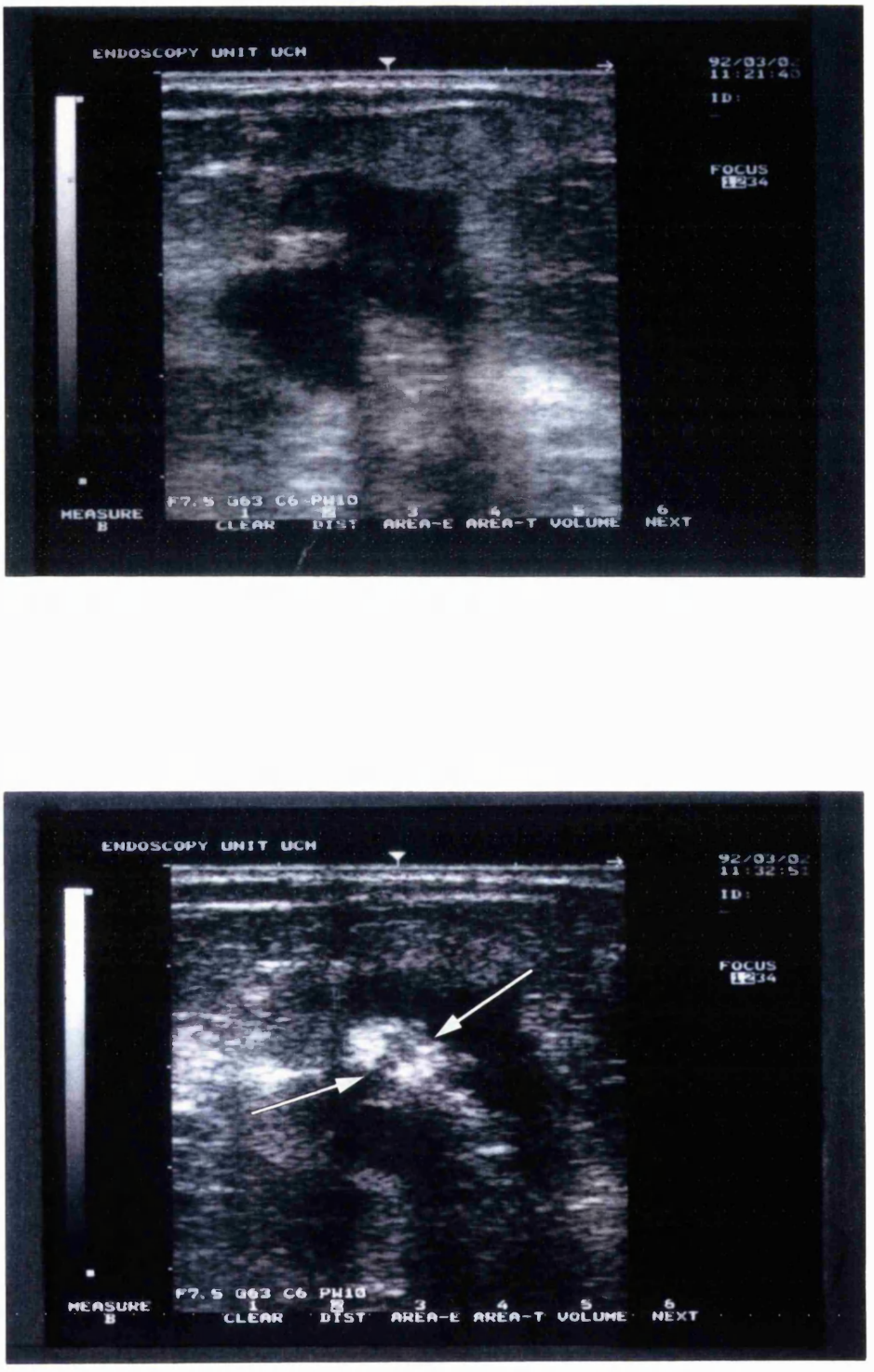


Figure 6.6: a)The tumour before treatment(above) and b)characteristic hyperthermic changes(arrowed) seen within the tumour during ILP treatment.

6.4 Statistical analysis

A Wilcoxon Rank Sum test using the Statview® programme(Abacus Concepts, Inc.) was used to compare the median diameter of necrosis when charring was present with the median diameter of necrosis attained in the absence of charring. Comparison was also made between the size of necrosis obtained by using a pre-charred fibre with that obtained by using a clean fibre.

Linear regression analysis was used to assess the correlation between the size of the tumour as measured by ultrasound and histology and the size of necrosis as measured by ultrasound and histology.

6.5 Results

Forty five patients underwent surgery after ILP and they varied in age from 45 to 85 years(mean 68years, median 72 years). All had early stage breast cancer($T_1G_1N_0$ to $T_2G_3N_1$). Ten patients underwent mastectomy(22%) and thirty five wide local excision of the tumour(78%). The interval between laser treatment and surgery varied between 1 and 94 days(mean 12 days, median 7 days). The patient who underwent surgery 94 days after ILP had originally refused surgery and eventually came to lumpectomy after 94 days, otherwise the interval varied from 1-34 days(mean 10 days, median 7 days). The laser power varied from 2-3 watts and the exposure from 500-750 seconds(treatment was abandoned early in 4 patients, see below). The patient details and the results are outlined in table 6.1. Twenty seven patients underwent ILP using a clean fibre and 18 using a pre-charred fibre.

6.5.1 Patient outcome and complications

The vast majority of patients undergoing ILP tolerated the procedure well although many did comment that they had a feeling of warmth in the breast during the procedure.

Treatment was stopped prematurely in four patients at 200, 360, 490 and 540 seconds due to pain. All of these patients underwent ILP utilising a clean fibre. One of these patients was extremely anxious and the tumour was near the skin and the other three had deep tumours and complained of pain radiating into the axilla presumably due to stimulation of the intercostal nerves. Three of these patients had evidence of laser damage in the resected specimen with areas of thermal necrosis of 6, 10 and 12mm whilst the fourth had no evidence of laser damage. Treatment was not curtailed in any of the patients who underwent ILP with a pre-charred fibre. One patient had a minor haemorrhage(less than 50mls) from the needle puncture site 2 hours after ILP which was easy to control. Another patient received a minor skin burn during ILP. This occurred at the site of entry of the needle as it passed through the skin and was caused by the laser fibre falling back slightly during treatment and causing the tip and then the shaft of the metal needle to heat up by thermal conduction. As the procedure was

performed under local anaesthesia the patient was unaware of any discomfort and the skin burn was not noted until the completion of treatment. This area healed well leaving a small scar which was excised along with the tumour at the time of surgery.

Forty four of the forty five patients are alive and free of local, regional and distant disease at a follow up ranging from 2 to 26 months. One patient has died of disseminated oesophageal carcinoma which presented six weeks after ILP.

6.5.2 Gross pathologic features associated with ILP treatment in breast cancers.

Following surgery the tumour was incised after inking of the specimen to assess the tumour margins. Charring was evident within the tumour in 12 patients and was not evident in 15 cases following the use of a clean fibre. Charring was present in 17 out of 18 of the tumours following the use of a pre-charred fibre and was noted at 1 day and at 34 days after ILP. The presence of charring in the resected tumour was associated with a larger diameter of necrosis when compared with the diameter found in the absence of charring(median 13 vs 6 mm, p= 0.002). Pre-charring the fibre resulted in a larger diameter of necrosis when compared with the diameter attained using a clean fibre(median 14 vs 10mm, p=0.002). There was no significant difference between the diameter of necrosis attained when using a pre-charred fibre and that attained when charring occured spontaneously(p=0.25) but pre-charring made the procedure more predictable. In four patients no evidence of laser damage could be found in the resected specimen and this occurred in three patients using a clean fibre and in one patient using a pre-charred fibre. The median diameter of necrosis attained in the presence or absence of charring and the diameters attained by using a clean or a pre-charred fibre are illustrated in figure 6.7. Typical appearences on cutting the tumour following ILP are shown in figures 6.8 and 6.9. The laser produced a roughly spherical lesion around the fibre tip and in those tumours which had evidence of charring, the area where the fibre tip had been left was a longitudinal cavity approximately 5-8mm long and 3-5mm in diameter. The wall of this cavity was lined in some cases by charred material and this was surrounded by an area of necrosis and a characteristic rim of haemorrhage

beyond which was either viable tumour or viable normal breast tissue. When charring did not occur spontaneously no cavity was visible and it was sometimes difficult to know where the laser fibre tip had been. A low power microscopic picture is seen in figure 6.10 showing a tumour 27 days after ILP using a pre-charred fibre.

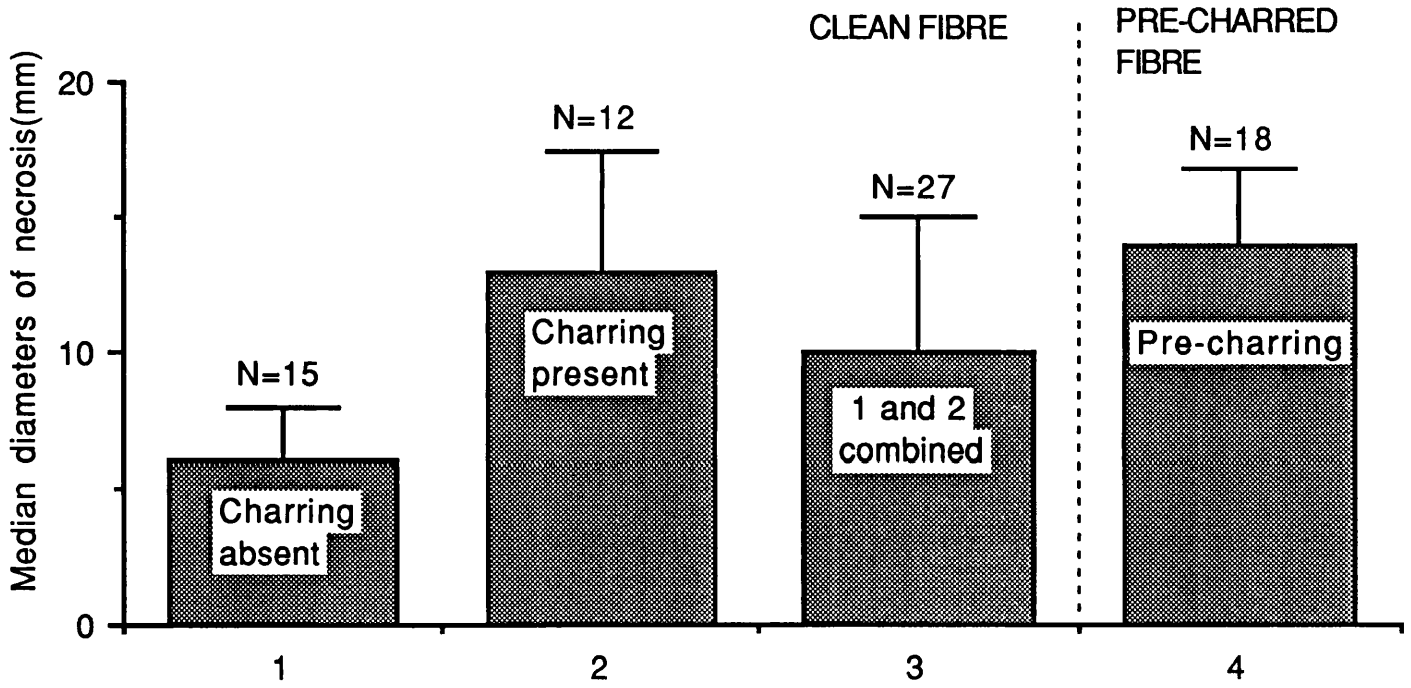


Figure 6.7: Diameters of necrosis(median and interquartile range)

Name	Age	Power	Exposure	Interval*	Charring	Tumour diam.	Necrosis	Histology**	Operation	Stage(TNM)
M.K.	70 yrs	2.5 Watts	500 secs	1 Day	No	35mm	6mm	IDC	WLE	T2 G3 Nx
V.C.	55 yrs	2.5 Watts	500 secs	2 Days	No	40mm	2mm	ILC	WLE	T2 G3 Nx
E.C.	78 yrs	2 Watts	500 secs	2 Days	No	30mm	Zero	IDC	Mastectomy	T2 G3 N1
M.G.	79 yrs	2 Watts	490 secs	94 Days	No	8mm	10mm	IDC	WLE	T1 G2 Nx
M.M.	51 yrs	3 Watts	200 secs	28 Days	No	20mm	6mm	IMC	Mastectomy	T1 Gx N1
P.G.	63 yrs	2.5 Watts	600 secs	6 Days	No	15mm	3mm	IDC	WLE	T1 G2 No
L.B.	54 yrs	2.5 Watts	500 secs	13 Days	No	17mm	3mm	IDC	WLE	T1 G2 No
M.O.	53 yrs	2.5 Watts	500secs	13 Days	No	11mm	8mm	IDC	Mastectomy	T1 G2 No
S.C.	85 yrs	2.5 Watts	600 secs	13 Days	No	21mm	10mm	IDC	WLE	T2 G1 No
D.A.	64 yrs	3 Watts	600 secs	1 Day	No	20mm	8mm	IDC	WLE	T1 G2 Nx
S.D.	45 yrs	2 Watts	750 secs	7 Days	No	13mm	Zero	ICC	WLE	T1 Gx No
D.T.	78 yrs	2 Watts	750 secs	8 Days	No	28mm	8mm	IDC	WLE	T2 G2 No
M.L.	65 yrs	2.5 Watts	600 secs	1 Day	No	20mm	6mm	IDC	WLE	T1 G1 Nx
H.D.	76 yrs	3 Watts	540 secs	14 Days	No	35mm	Zero	DCIS	WLE	Tis Gx No
J.H.	72 yrs	2.5 Watts	600 secs	6 Days	No	18mm	12mm	IDC	Mastectomy	T1 G2 N1
M.M.	75 yrs	2.5 Watts	500 secs	6 Days	Yes	42mm	12mm	IMC	WLE	T2 Gx No
L.P.	76 yrs	2.5 Watts	600 secs	13 Days	Yes	20mm	20mm	ICC	WLE	T1 Gx No
P.J.	62 yrs	2.5 Watts	360 secs	7 Days	Yes	40mm	12mm	IDC	Mastectomy	T2 G2 N1
H.H.	83 yrs	2.5 Watts	500 secs	11 Days	Yes	30mm	15mm	IDC	Mastectomy	T2 G3 N1
E.R.	74 yrs	2.5 Watts	750 secs	20 Days	Yes	22mm	13mm	IMC	Mastectomy	T2 Gx No
A.D.	55 yrs	2 Watts	750 secs	1 Day	Yes	20mm	13mm	IDC	WLE	T1 G2 Nx
M.B.	79 yrs	2.5 Watts	750 secs	10 Days	Yes	25mm	13mm	ILC	WLE	T2 Gx No
J.A.	74 yrs	3 Watts	600 secs	6 Days	Yes	25mm	8mm	IDC	WLE	T2 Gx Nx
P.B.	78 yrs	2 Watts	500 secs	12 Days	Yes	25mm	11mm	DCIS	WLE	Tis Gx Nx
S.H.	51 yrs	2.5 Watts	500 secs	3 Days	Yes	25mm	10mm	IDC	WLE	T2 G3 N1
A.V.	81 yrs	3 Watts	600 secs	6 Days	Yes	26mm	25mm	IPC	WLE	T2 Gx No
I.S.	74 yrs	3 Watts	600 secs	6 Days	Yes	26mm	23mm	IDC	WLE	T2 G1 No

Table 6.1 ILP patient details and results

Name	Age	Power	Exposure	Interval*	Charring	Tumour Diam.	Necrosis	Histology **	Operation	Stage(TNM)
M.S.	51 yrs	2.5 Watts	500 secs	13 Days	Pre-charred	Not available	20mm	IDC	WLE	Tx Gx No
G.M.	73 yrs	2.5 Watts	500 secs	18 Days	Pre-charred	Not available	25 mm	ITC	WLE	Tx Gx No
D.C.	53 yrs	2.5 Watts	500 secs	17 Days	Pre-charred	20mm	20mm	IDC	WLE	T1 G2 No
V.B.	71 yrs	2.5 Watts	500 secs	20 Days	Pre-charred	Not available	25mm	LCIS	WLE	Tx Gx No
B.B.	73 yrs	2.5 Watts	500 secs	34 Days	Pre-charred	26mm	14mm	IDC	WLE	T2 G1 N1
Y.P.	72 yrs	2.5 Watts	500 secs	6 Days	Pre-charred	12mm	12mm	IMC	WLE	T1 Gx No
L.K.	85 yrs	2.5 Watts	500 secs	15 Days	Pre-charred	21mm	6mm	IDC	WLE	T2 G2 No
M.R.	76 yrs	2.5 Watts	500 secs	19 Days	Pre-charred	30mm	14mm	IDC	WLE	T2 G3 N1
G.S.	68 yrs	2.5 Watts	500 secs	4 Days	Pre-charred	40mm	12mm	IDC	Mastectomy	T2 G3 N1
B.F.	52 yrs	2.5 Watts	500 secs	1 Day	Pre-charred	15mm	9mm	ICC	WLE	T1 Gx No
V.M.	53 yrs	2.5 Watts	500 secs	6 Days	Pre-charred	19mm	16mm	IDC	WLE	T1 G3 N1
R.M.	78 yrs	2.5 Watts	500 secs	6 Days	Pre-charred	24mm	15mm	IDC	WLE	T2 G2 Nx
J.F.	80 yrs	2.5 Watts	500 secs	27 Days	Pre-charred	29mm	18mm	IDC	WLE	T2 G2 N1
P.S.	58 yrs	2.5 Watts	500 secs	5 Days	Pre-charred	35mm	12mm	ILC	Mastectomy	T2 Gx N1
M.o'S.	47 yrs	2.5 Watts	500 secs	4 Days	Pre-charred	18mm	Zero	IDC	Mastectomy	T1 G2 No
M.L.	77 yrs	2.5 Watts	500 secs	27 Days	Pre-charred	23mm	12mm	IDC	WLE	T2 G2 N1
O.B.	51 yrs.	2.5 Watts	500 secs	7 Days	Pre-charred	30mm	9mm	IDC	WLE	T2 G2 N1
E.E.	80 yrs.	2.5 Watts	500 secs	4 Days	Pre-charred	28mm	19mm	IDC	WLE	T2 G2 No

Table 6.1 ILP patient details and results

Legend to table 6. 1

* Interval refers to the interval between laser treatment and subsequent surgery in days.

Charring refers to whether charring was noted in the tumour on sectioning after surgery

Tumour diameter indicates the size of the tumour as measured microscopically.

Necrosis indicates the size of the laser induced area of necrosis as measured microscopically

** Refers to the histological type of the excised tumour.

IDC Invasive ductal carcinoma

DCIS Ductal carcinoma in situ

ILC Invasive lobular carcinoma

LCIS Lobular carcinoma in situ

ICC Invasive cribriform carcinoma

IMC Invasive mucinous carcinoma

IPC Invasive papillary carcinoma

ITC Invasive tubular carcinoma

The stage is based on the TNM classification, G referring to the Bloom and Richardson classification.

WLE refers to wide local excision.

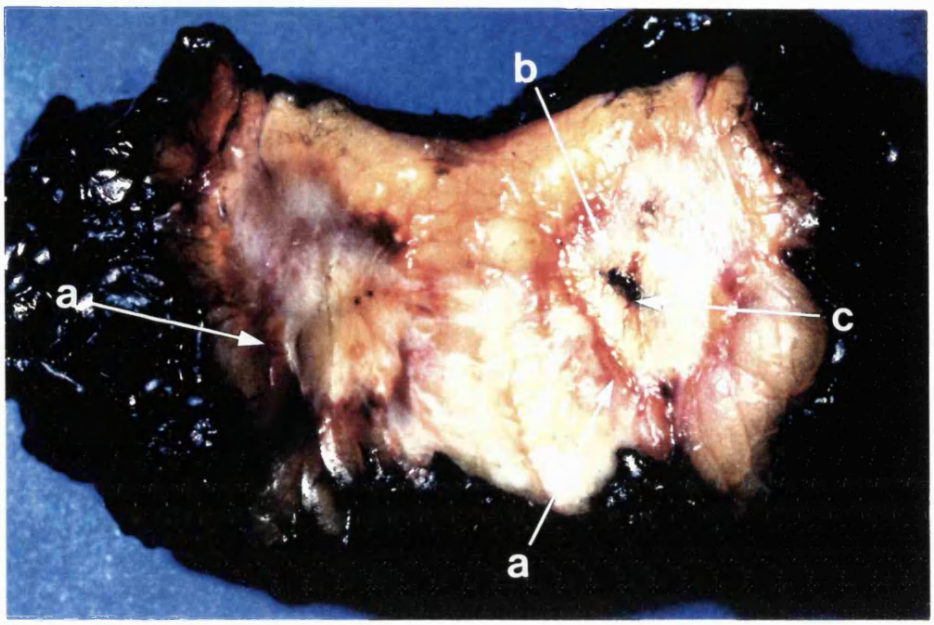


Figure 6.8: A resected specimen(cut through the centre and opened) 24 hours after ILP and 30 minutes following surgery(2 watts, 750 seconds using a clean fibre) The specimen has been inked to assess the resection margins. a) the characteristic rim of haemorrhage b) the area of necrosis c) charring present within the tumour at the site of the laser fibre tip.

Figure 6.9: The resected specimen 3 days after ILP(2.5 watts, 500 seconds using a clean fibre). The area of laser damage is roughly spherical in shape. a) area of necrosis b) normal breast tissue c) rim of haemorrhage d) cavity with charring at the site of the fibre tip.

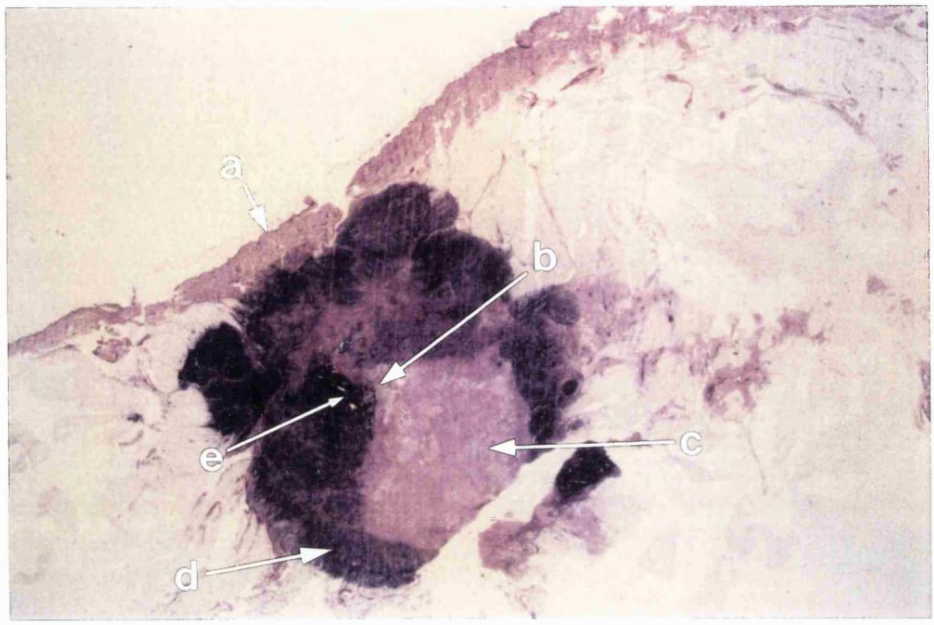


Figure 6.10: Low power microscopic view of a resected cancer 27 days after ILP using a pre-charred fibre(2.5 watts, 500 seconds) a)skin b) position of the fibre tip c) area of necrosis d) viable tumour e) charring.

6.6 Discussion

If ILP is to be an effective alternative to lumpectomy it must be both predictable, in terms of its ability to produce necrosis, and safe. Initially, we used a clean laser fibre which in normal homogenous liver produced predictable diameters of necrosis of up to 16mm(Mathewson et al, 1987). However when we placed a clean laser fibre into a breast cancer the technique was far from predictable as can be seen in Figure 6.7 where the Y error bars are widely spaced indicating the great variation in tumour response. In 4 patients no evidence of laser damage was evident in the resected tumour. In one of these patients ILP was abandoned early due to pain but no reason could be found to explain the lack of necrosis in the other three. The variation in response of the tumours to the same or similar laser parameters is evident in table 6.1 where the laser damage varied from 0-25mm when using a clean fibre. This difference is most probably due to the differing optical properties of breast tumours which are inhomogenous, reflecting and absorbing light at different rates depending upon their constituents and the vascularity of the tumour. It is also conceivable that tumours have differing optical properties within each individual tumour depending upon the amount of calcification, necrosis and haemorrhage within it. Key et al(1991) have shown that fibroglandular breast tissue and fatty breast tissue have different optical properties and that breast carcinomas have optical properties similar to fibroglandular tissue at 700nm. Nakamura et al(1990) demonstrated a difference in the optical properties of normal liver and malignant liver tumours. It is also known that the tissue vascularity(Jacques et al,1992) and tissue inhomogeneities(Svaasand et al,1985) can effect the optical properties a situation that is complicated further by the observation that tissues are able to change their optical properties during ILP(Essenpreis et al,1991). It is most probably for these reasons that ILP using a clean fibre gave unpredictable results but further studies analysing the optical properties of breast cancers would confirm this.

The most important factor influencing the extent of necrosis found in this work has been the presence or absence of charring around the fibre tip at the end of treatment. In the presence of charring there was significantly more necrosis than when it was

absent(median 13 vs 6 mm). Charring did not appear to be energy or power dependent at the values used in this study and again the reasons why it occurs in some, but not other tumours, is not immediately obvious. Although there is no significant difference between the diameter of necrosis when charring occurs spontaneously and that attained by pre-charring the fibre, pre-charring does make the effect more predictable as evident by the results set out in table 6.1 and figure 6.1 where the Y error bars are small indicating little variation in necrosis. The importance of charring has been demonstrated by Wyman et al(1992) who noted that charring results in larger areas of necrosis in bovine muscle and concluded that once it has occurred the rest of the process is perpetuated by thermal conduction. Amin et al(1993a) have also shown a strong association between charring and a larger diameter of necrosis in rat liver *in vivo.* and demonstrated how by using a pre-charred fibre a larger diameter of necrosis could be obtained(using the Nd:YAG laser at 1064nm but not using the diode laser as spontaneous charring occurred with all diode laser lesions) It was as a result of this work and the observation that charring was significantly associated with a larger diameter of necrosis that we conducted the further study using the pre-charred fibre. Pre-charring made the technique of ILP much more predictable. The laser fibre tip was essentially acting as a point heat source causing the heat to be dissipated into the surrounding tumour tissue by thermal conduction. The most likely reason why the technique of pre-charring resulted in more predictable diameters of necrosis was that the necrotic damage occurred purely by thermal rather than optical mechanisms. The thermal properties of tissues are largely water dependent and as water is the main constituent of tissues then the thermal properties vary little from tissue to tissue, hence a more predictable response, whereas the optical properties of tissues as already mentioned vary considerably. Pre-charring the fibre is a relatively straight forward technique but would be easier if commercially made pre-charred fibres were available.

Although pre-charred fibres have shown promise in this work it may be possible to increase the necrotic lesion diameter even further by using a modified fibre tip such as the diffuser tip modification described by Nolsoe et al(1992) where lesions of up to

44mm in diameter were produced in pig livers. A major specification of any fibre modification is that they must be transmissible down the bore of a 14G cannula(a problem with the sapphire tip fibres). Fibre modifications such as that described by Nolsoe et al(1992) could be compared with a pre-charred fibre for the breast work and further studies are awaited.

CHAPTER 7: HISTOPATHOLOGICAL EFFECTS OF ILP ON BREAST CANCER AND ADJACENT NORMAL BREAST TISSUE.

7.1 Introduction

The histological subtypes of tumours are outlined in table 6.1. There were 30 invasive ductal carcinomas(4 grade I, 18 grade II, 7 grade III and in 1 patient the tumour was ablated to such a degree by ILP that grading was not possible), 3 invasive lobular carcinomas, 3 invasive cribriform, 1 invasive tubular, 4 invasive mucinous and 1 invasive papillary carcinoma. Two patients had tumours composed purely of ductal carcinoma in situ without invasion and 1 patient a purely lobular carcinoma in situ (although the tumour was largely ablated by the laser treatment and so accurate assessment of tumour type was not possible). No medullary carcinomas were included. The maximum diameter of the tumour varied from 8-42 mm. In 3 patients it was not possible to accurately assess all the microscopic boundaries of the tumour due to the damage caused by ILP. The implications of such complete tumour ablation are discussed in detail in the discussion(section 7.4)

7.2 Microscopic features of ILP induced necrosis in breast cancers

Microscopically distinct zones existed adjacent to the area around the cavity left by the laser fibre. In those who were noted to have charring a blackened area of char lined the cavity and this cavity will be called zone A. This cavity was sometimes without apparent contents and sometimes contained necrotic debris. The wall of the cavity consisted sometimes of charred tissue which was often admixed with distorted clumps of carcinoma cells that possess very elongated nuclei, a characteristic feature seen in diathermy artefact.

Just outside zone A and extending circumferentially around it is a zone showing good morphological preservation of both epithelial and connective tissue elements (to be called zone B). We have called this area an area or zone of in situ fixation. The only evidence of tissue damage in this area are occasional areas of neoplastic epithelium showing diathermy artefact namely elongation of the nucleus and an elongated spindle like appearence to the cells(figure 7.2). In other areas the in situ fixated tumour tissue

was indistinguishable from viable tumour(figure 7.3). This zone was consistently present at one day and was seen in the specimen resected at 94 days after ILP. Zone B was seen in the presence of charring, the absence of charring and following the use of a pre-charred fibre. There was no evidence of an acute inflammatory response at the interface between the in situ fixation and the surrounding necrotic tissue and the area appeared well preserved with no evidence of necrosis in the tumours resected at 27 days, 34 days and 94 days after ILP. The area of the cavity, the area of in-situ fixation and the surrounding necrotic tissue are seen in figure 7.1, 7.2, 7.3 and 7.4.

Tissue surrounding zone B (to be called zone C) shows haemorrhagic necrosis of neoplastic epithelium and its associated connective tissue stroma(figure 7.5). It is the loss of the structural integrity of blood vessels in this zone that causes the extensive haemorrhage seen macroscopically. The cells in this area showed evidence of pyknosis, karyorrhexis and karyolysis(figure 7.5). This left a necrotic zone with many cells lacking a nucleus, a feature which conferred a ghost cell appearance. This necrotic area was also consistently present at up to 34 days after ILP although the haemorrhagic element was most marked in the first few days after treatment and became less marked with time as the blood was resorbed. In one case extensive thrombosis was seen in vessels surrounding zone C three days after treatment(figure 7.6).

Zone C consists of an inner area with haemorrhagic necrosis and an outer area interfacing with the surrounding viable tissue(which was either tumour or normal breast fat). At the edge of zone C where it interfaced with unaffected surrounding tissue an acute inflammatory respone was evident initially admixed with an area of haemorrhage(figure 7.7). Interspersed between these cells(the necrotic cells in zone C and the cells of the surrounding viable tissue) initially an acute inflammatory reaction was evident in the outer part of zone C which by five days was accompanied by healing in the form of granulation tissue(figure 7.8). The area of granulation tissue gradually expanded(figure 7.9) such that at 34 days a significant amount of granulation tissue was evident and by 94 days(figure 7.10) a fibrotic mass with peri-ductal elastosis,

endarteritis and fat necrosis was evident. A foreign body giant cell response was evident in specimens resected 27-94 days after ILP(figure 7.11) and calcification was evident in the wall of the cavity in the specimen resected 94 days after ILP. The following flow diagram simplifies the histopathological changes that occur with time after ILP(figure 7.12).

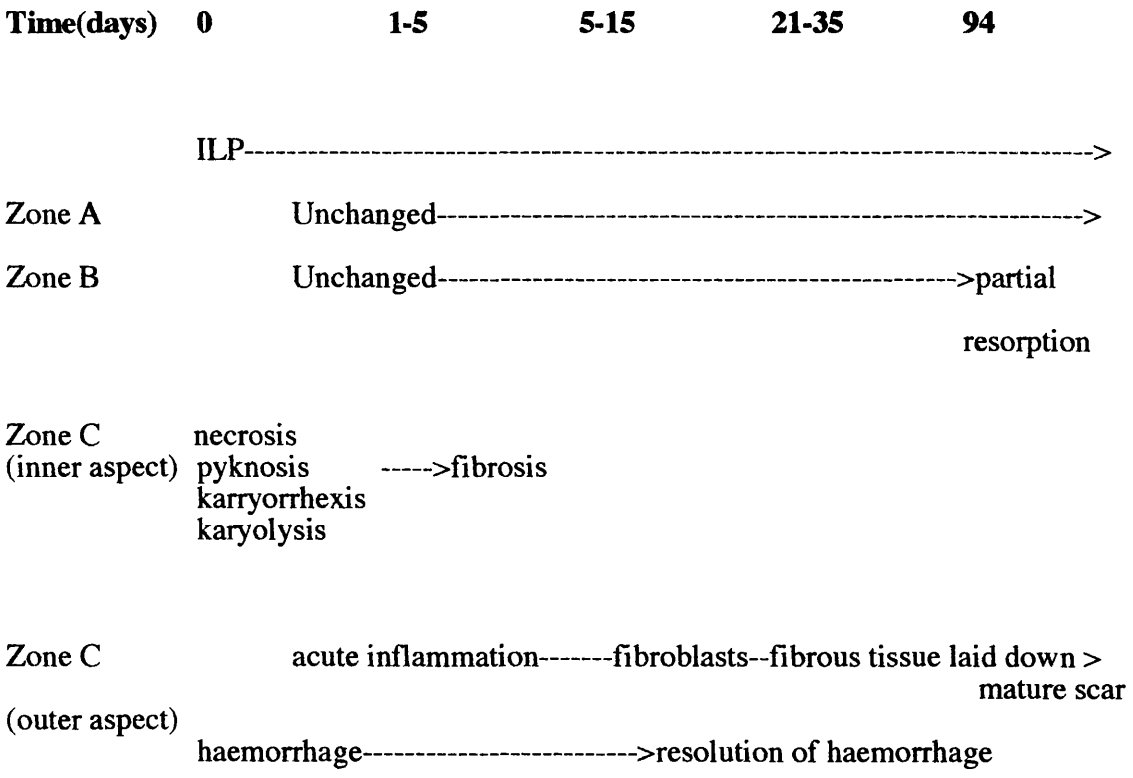
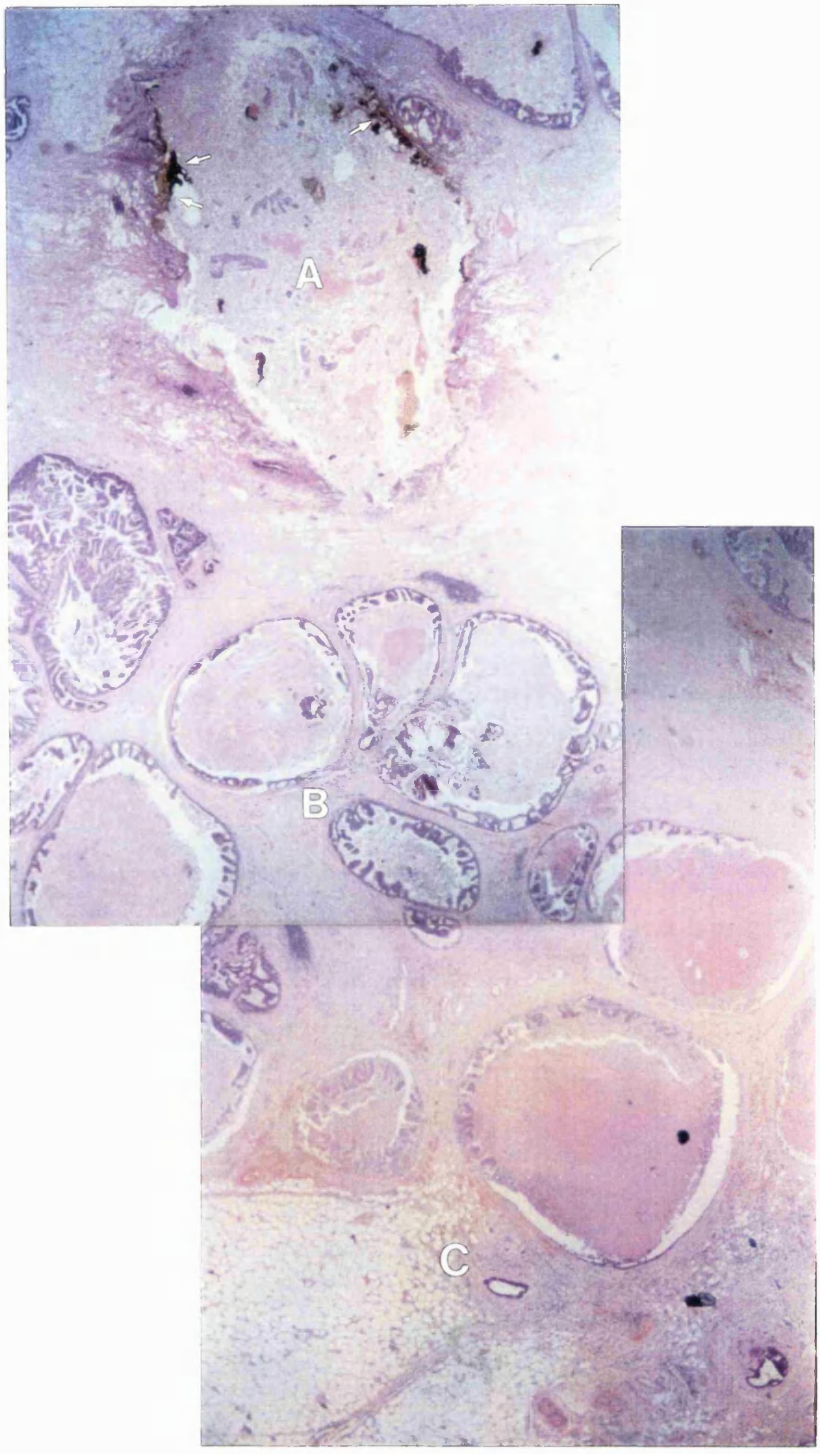


Figure 7.12: Flow diagram of histopathological changes that occur after ILP in breast cancers.

Figure 7.1: The cavity(A) with evidence of charring lining the cavity(arrowed), the area of in situ fixation(B) and surrounding necrosis(C) seen in a tumour excised 12 days after ILP using a clean fibre at 2 watts for 500 seconds.



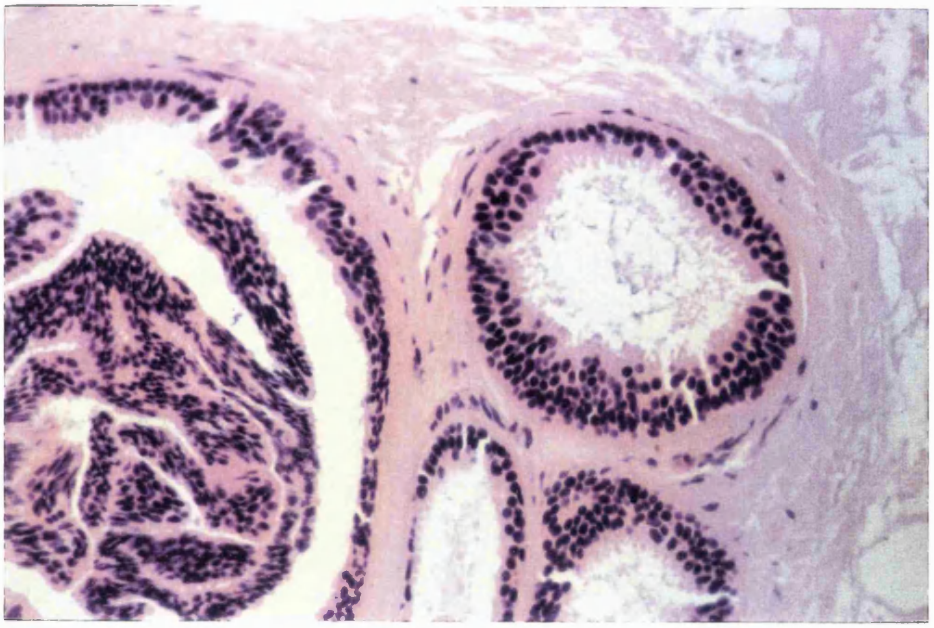


Figure 7.2: The area of *in situ* fixation in greater detail(same specimen as figure 7.1) showing elongation of the nuclei and spindle like cells in a patient with a pure ductal carcinoma in situ.

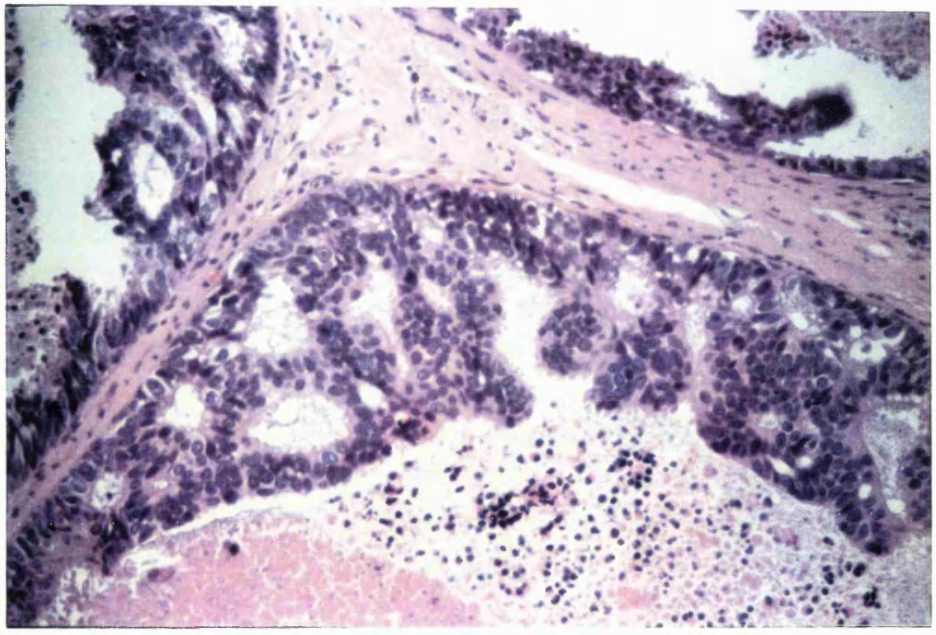


Figure 7.3: In areas, the zone of *in situ* fixation(same specimen as figure 7.1) did not differ in appearance from viable tumour tissue. This figure shows an area of ductal carcinoma in situ within zone B.

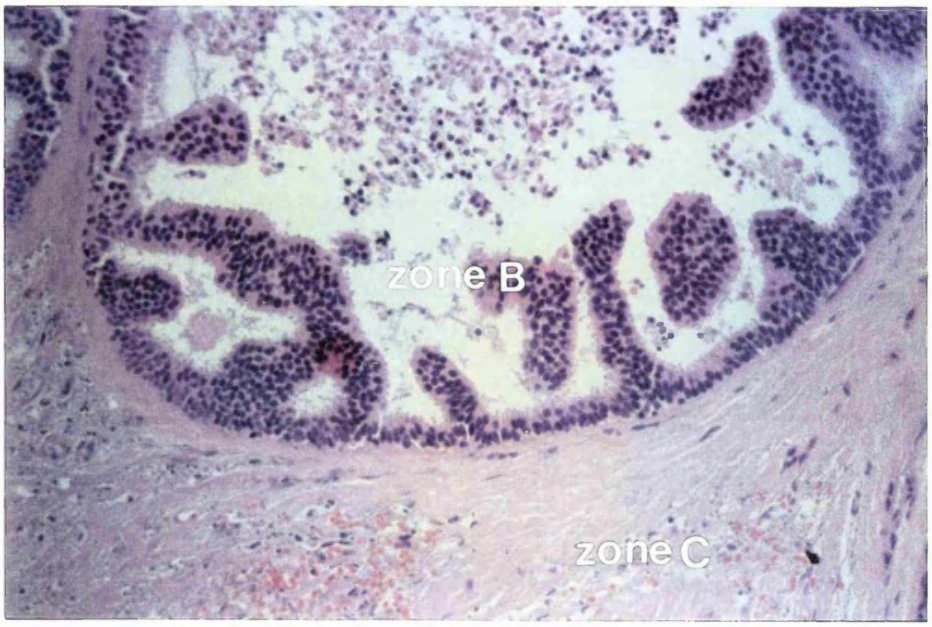


Figure 7.4: The junction between the *in situ* fixation and necrotic tissue 12 days post ILP, there is no evidence of inflammation.

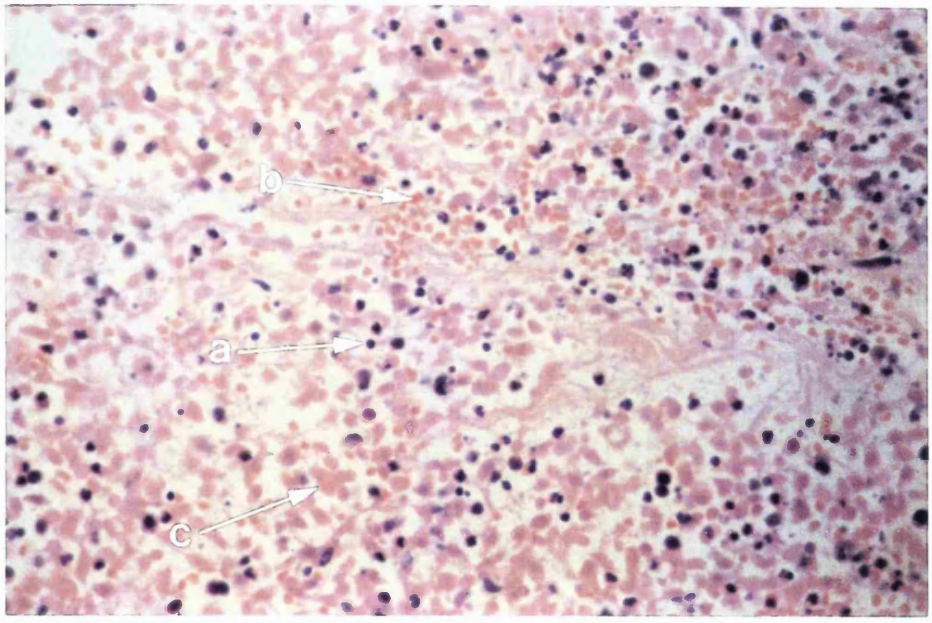


Figure 7.5: The zone of necrosis(zone C) showing a) pyknotic cells b) haemorrhage c) ghost like cells after karyolysis 3 days after ILP using a clean fibre 2.5 watts for 500 seconds.

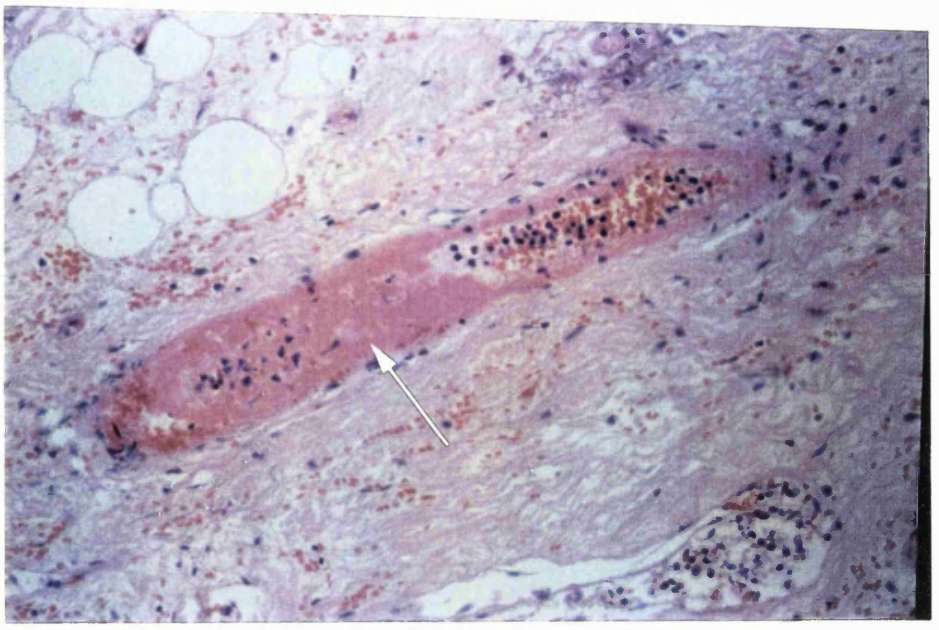


Figure 7.6: Thrombosis evident 3 days after ILP in the outer aspect of zone C(arrowed). The laser was activated at 2.5 watts for 500 seconds using a clean fibre.

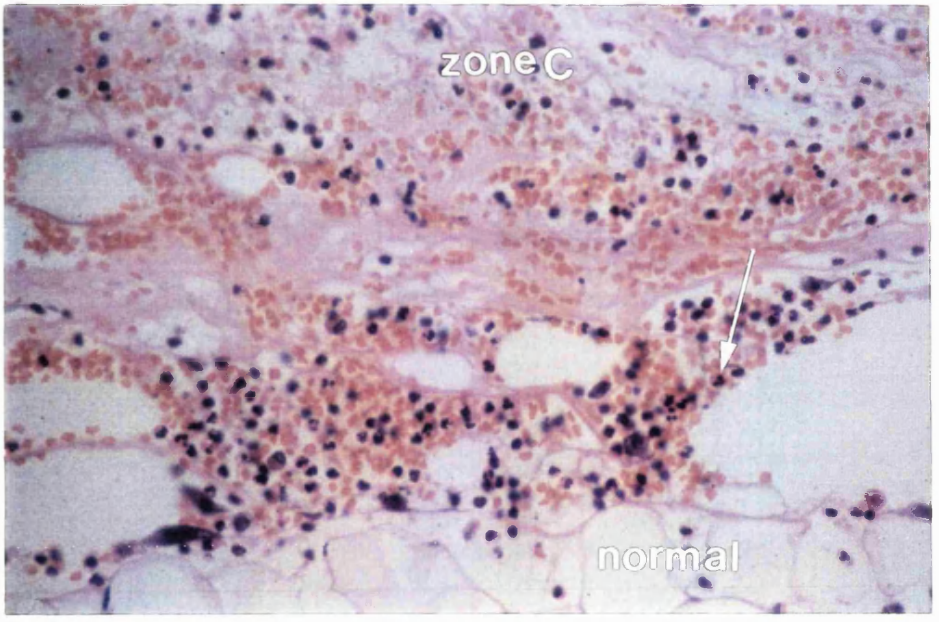


Figure 7.7: Acute inflammatory response(polymorph arrowed) at the interface between necrotic tumour(zone C) and normal tissue 3 days after ILP using a clean fibre, 2.5 watts for 500 seconds.

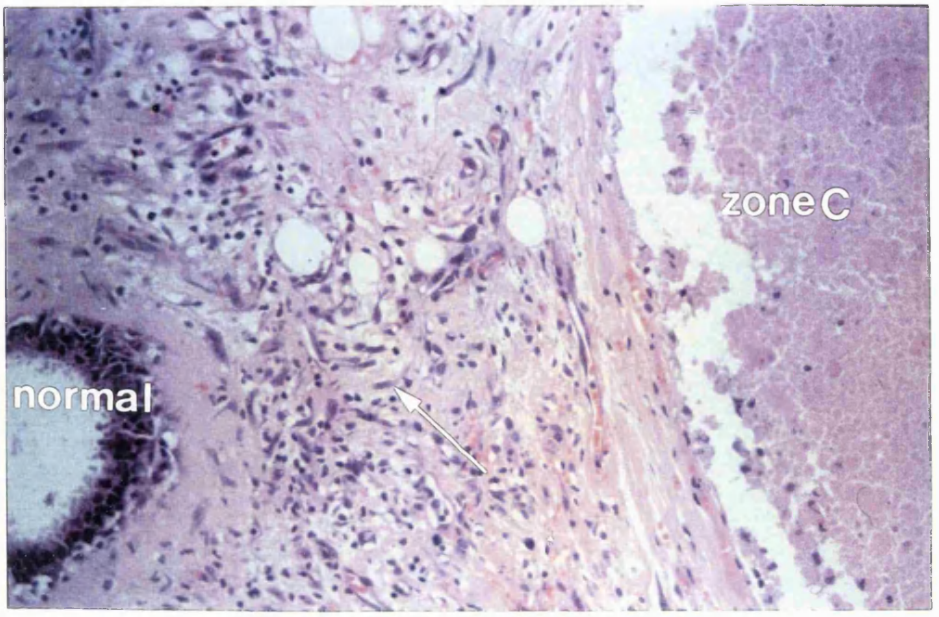


Figure7.8:Junction between zone C and normal breast tissue 7 days after ILP(fibroblasts arrowed)

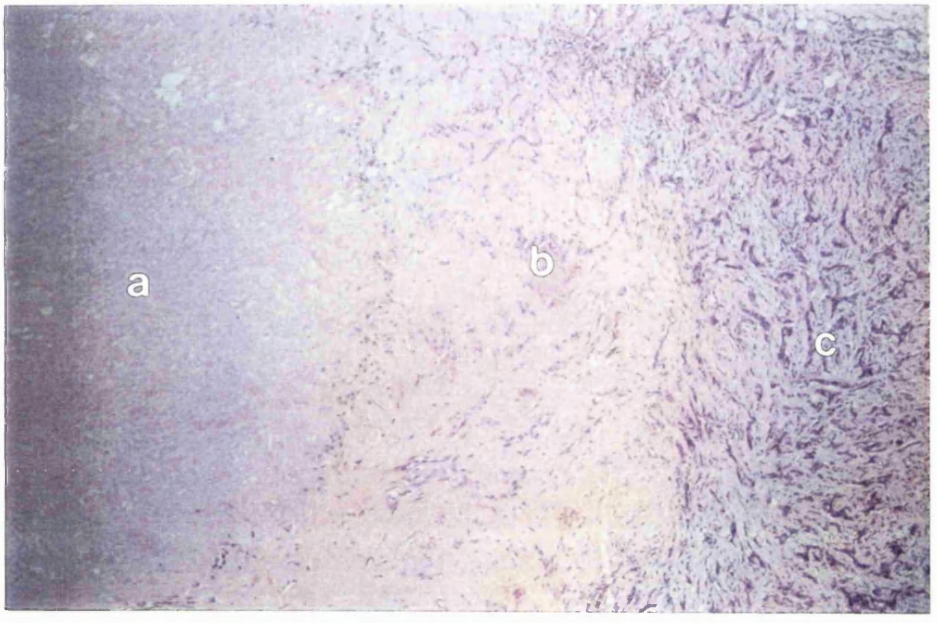


Figure 7.9:The area of granulation tissue gradually expands. A resected specimen 27 days after ILP. a) necrosis b)granulation tissue and c)viable tumour.

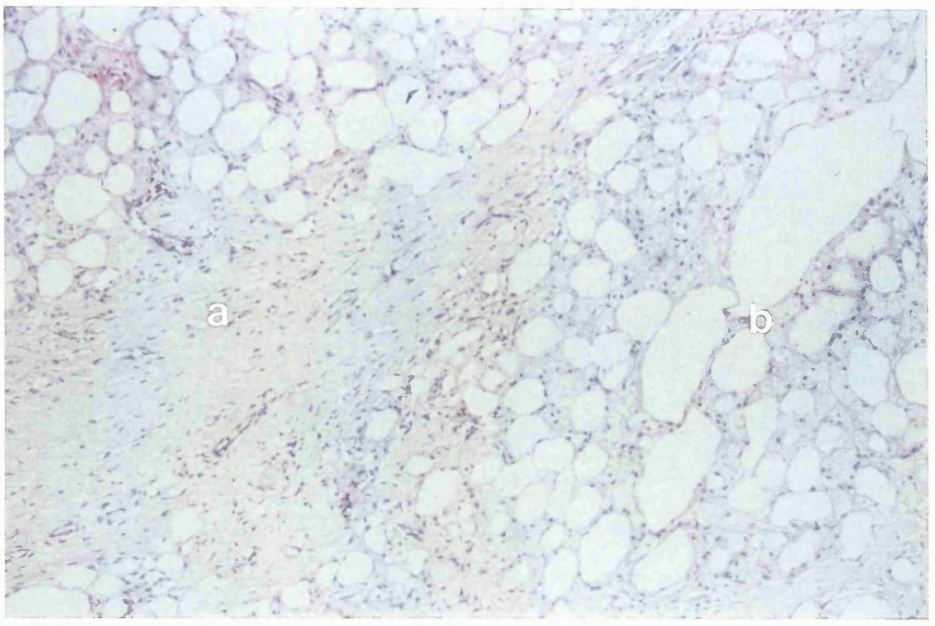


Figure 7.10: The resected tumour 94 days after ILP, a) fibrous tissue and b) fat necrosis.

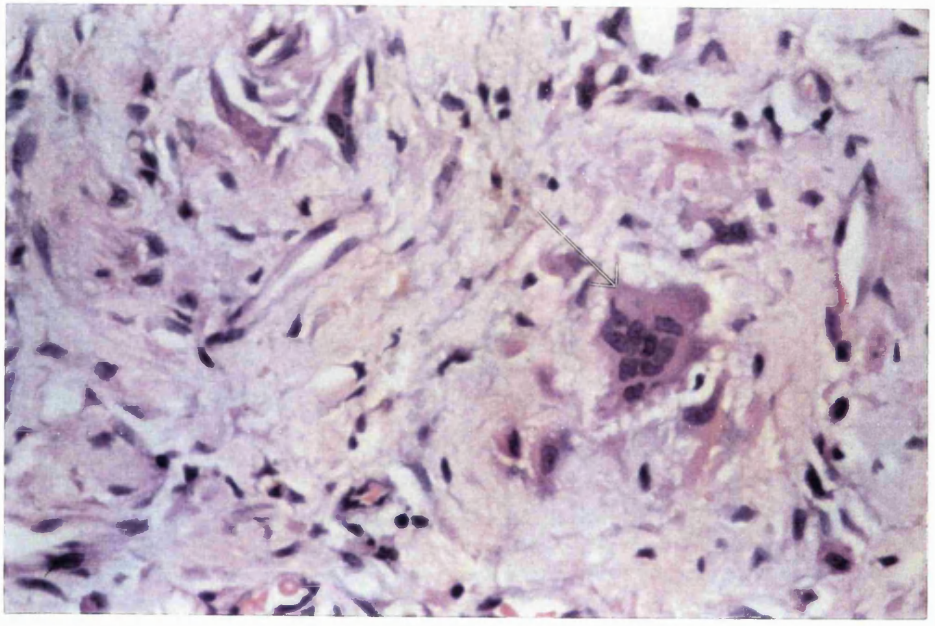


Figure 7.11: A foreign body giant cell response(arrowed) evident 27 days after ILP.

6.6.3 Effect of ILP on normal breast tissue

In several of the tumours laser damage was noted to histologically normal breast tissue adjacent to the tumour. The phenomena of in situ fixation has not been seen in normal breast tissue per se, probably because normal breast tissue was never close enough to the fibre, however there does appear to be evidence of in situ fixation of small blood vessels within normal and neoplastic tissue. A range of effects was noted in normal breast ranging from acellular fat necrosis near to the area of laser damage passing through an area of fat necrosis with evidence of histiocytes and phagocytes through to an area of normal fatty breast tissue. Very little damage was noted to normal epithelial and glandular breast tissue in this series(possibly because many of the patients were post menopausal and the breast was largely fatty) and it is therefore not possible to comment on healing of laser effects in normal breast.

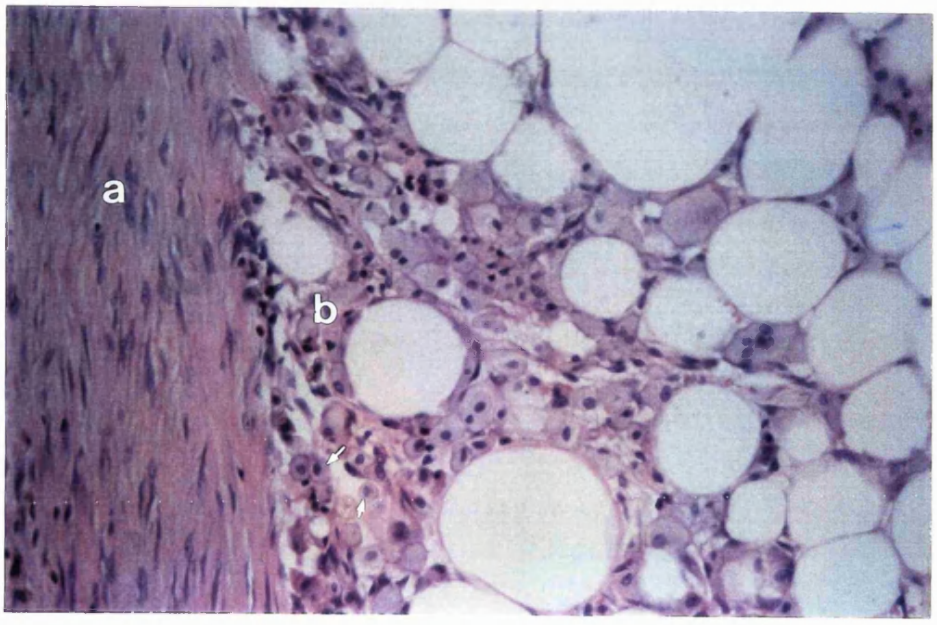


Figure 7.13: Effect of ILP on normal breast tissue 1 day after ILP a) normal breast stroma b) fat necrosis with foamy macrophages(arrowed)

7.4 Discussion

The histological appearances of the tumour following ILP are similar to those noted in the experimental rat liver by Mathewson et al(1987) and in pig liver by Dachman et al(1990) and Bosman et al(1991). Mathewson et al(1987) noted an area of coagulative necrosis adjacent to a central charred area with a dense inflammatory response adjacent to this coagulative necrotic zone and then a zone of undamaged tissue. Adjacent to zone A(the central charred cavity) we have described this area of apparently preserved and viable tumour tissue(zone B), the only evidence of tissue damage being elongation of the nuclei and a spindle shaped appearance to the cells. These features in cells are due to heat artefact and have been described by Thomsen(1991). In other areas within this zone there was no evidence of tissue damage. If the well preserved morphological appearances seen in this area reflect tissue viability then the rationale for this form of laser therapy is undermined. It is far more likely that this morphologically well preserved tissue has occurred as a consequence of tissue fixation occurring *in-situ* at the time of ILP and that this tissue is non viable. Thermal induced fixation is a well recognised phenomenon that is occasionally used in the laboratory in the form of microwave fixation if rapid processing of tissue is required. Further evidence of *in situ* fixation resulting in a morphologically preserved, non viable tissue comes from three observations. Firstly, if this area was initially viable the circumferential necrosis surrounding it in zone C would prevent any vascular perfusion resulting in ischaemic necrosis. Secondly, the presence of focal diathermy artefact in zone B, a change implying severe structural damage to the nucleus, does not appear to result in the necrosis of affected cells, even days after the original laser insult. Finally if this area were viable then one would expect an area of acute inflammation in the interface between viable and necrotic tissue i.e. between zone B and zone C. No evidence of inflammation was noted in the interface between these zones but was noted in the interface between the non viable zone C and the surrounding viable tumour or normal tissue.There is then indirect evidence of laser induced fixation *in situ*.. A demonstration of a lack of biosynthetic activity in zone B by an inability, for example, to incorporate bromodeoxyuridine or NADPH diaphorase would provide more definitive evidence.

Thurell et al(1994) have demonstrated this area of *in-situ* fixation in experimental rat liver following ILP and have shown that it is non viable by virtue of the fact that it does not stain with NADPH diaphorase enzyme. This provides further evidence that this area(zone B) is in fact non-viable.

Zone C, the area of coagulative necrosis consisted of haemorrhage admixed with necrotic cells. Initially the nucleus of these cells was pyknotic prior to undergoing karolysis and in time once the nucleus has undergone karyorhexis the nucleus disappeared, an observation made in rabbit brain by Schatz et al(1992). During days 1-3 at the junction between zone C and viable tumour or normal tissue we observed an acute inflammatory reaction. Mathewson et al(1987) noted that the dense inflammatory zone was present by the fourth day although we have observed polymorphs at one day(the shortest time interval between ILP and surgery in this series) which have largely disappeared by 5 days after ILP.

The appearance of granulation tissue in the outer aspect of zone C by 5-7 days suggests that the treated tumour will eventually respond to ILP in a similar fashion to the experimental rat liver developing into a hard fibrous area(Mathewson et al,1987). This is supported by the observation in one tumour of a moderate amount of granulation tissue present in the outer aspect of zone C at 27 days and in the patient who underwent surgery 94 days after ILP dense fibrous tissue was evident in the tumour together with elastosis, endarteritis and fat necrosis. If the treated tumour were to form a hard fibrous nodule then this could lead to problems in the follow up of these patients as it may prove difficult to differentiate treated from untreated or recurrent tumour. FNAC of the tumour site together with a suitable imaging technique may be able to differentiate treated from untreated tumour(discussed in further detail below). If the treated area eventually heals with the formation of a fibrous area it is also possible that this scarring could produce deformity of the breast. This has not been observed in any of our patients following ILP although the follow up was short with the median time from ILP to surgery being only 7 days .

The appearance of fibrous tissue within the ILP treated area and the assumption that this area will heal into a fibrous(presumably hard) area would not only cause concern for the attending surgeon but may also engender anxiety and possibly significant psychological morbidity in the patient. It is only an assumption that all or most patients with even a small breast cancer would choose ILP in preference to conventional surgery. We have seen in chapter 2 that lumpectomy is by no means the automatic choice of all patients with breast cancer even if they were suitable for conservation, coupled with the report of Fallowfield et al(1986) who have shown that those women treated by conservation may in fact have higher levels of psychological morbidity than those who undergo mastectomy because of the fear of local recurrence. The patient treated with ILP may present with a hard lump in the breast, be treated by ILP and radiotherapy and still be left with a hard fibrous lump, this could lead to significant psychological morbidity and further studies(if ILP were to be available) could be aimed at identifying those patients who may be suitable for ILP and identifying ways to reduce psychological morbidity .

CHAPTER 8 : THE IMAGING OF INTERSTITIAL LASER PHOTOCOAGULATION IN BREAST CANCERS.

8.1 Ultrasound

8.2 Computerised Tomography(CT)

8.3 Magnetic Resonance Imaging(MRI)

8.4 Discussion

8.1 Ultrasound

Ultrasound was used in real time in 43 patients. Ultrasound allowed correct placement of the needle and hence the laser fibre within the tumour in all patients. Comparison of the maximum diameter of the tumour as measured by ultrasound and histology is outlined in figure 8.1($r=0.6$, $p=<0.001$). The results are shown for 35 patients. In five patients the tumour was not clearly visualised on ultrasound and in a further three the tumour was largely ablated by the laser and so accurate tumour size could not be measured histologically. Comparison of the maximum diameter of thermal changes seen on ultrasound and histology are outlined in figure 8.2($r=0.3$, p=N.S.) The correlation therefore between the maximum hyperechoic area seen by ultrasound during ILP and the final histology was poor with ultrasound tending to underestimate the final extent of necrosis in the majority of patients as illustrated in figure 8.3 and figure 8.4.

A gradually expanding hyperechoic region appeared adjacent to the needle tip 20-30 seconds after the start of treatment. The hyperechoic area was roughly spherical in shape with ill defined echogenic edges often having a dense hyperechoic centre and a less dense hyperechoic halo around it. This hyperechoic area expanded to reach a peak between 300 and 500 seconds into treatment and remained approximately the same size and shape until the end of therapy. Microbubbles were evident on ultrasound in some patients during treatment radiating from the dense hyperechoic area outwards(these bubbles are thought to represent small "packages" of steam caused by tissue water boiling). At the cessation of treatment the hyperechoic area gradually died away such that 5 minutes after treatment the laser treated area was indiscernible from untreated tumour(i.e.it becomes more heterogenous with similar echogenic appearances to untreated tumour). The changes seen during ultrasound typified in figure 8.3 were by no means consistent. Sometimes very little in the way of hyperechoic changes were evident and in some cases no hyperechoic changes were visible at all during ILP. Figure 8.4 shows again how in one case only minor hyperechoic areas were visible during ILP and yet this patient had 25mm of necrosis including some damage to surrounding normal breast tissue which was not visible on ultrasound.

Figure 8.1: Comparison of tumour size as measured by ultrasound and histology.

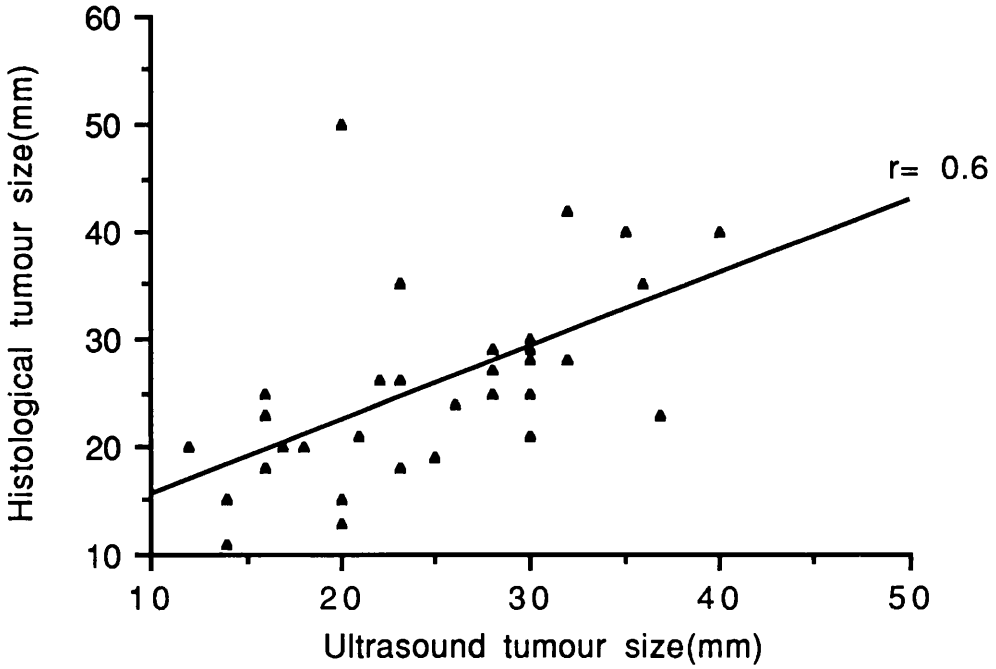


Figure 8.2: Comparison of the hyperechoic area seen on ultrasound and histological necrosis

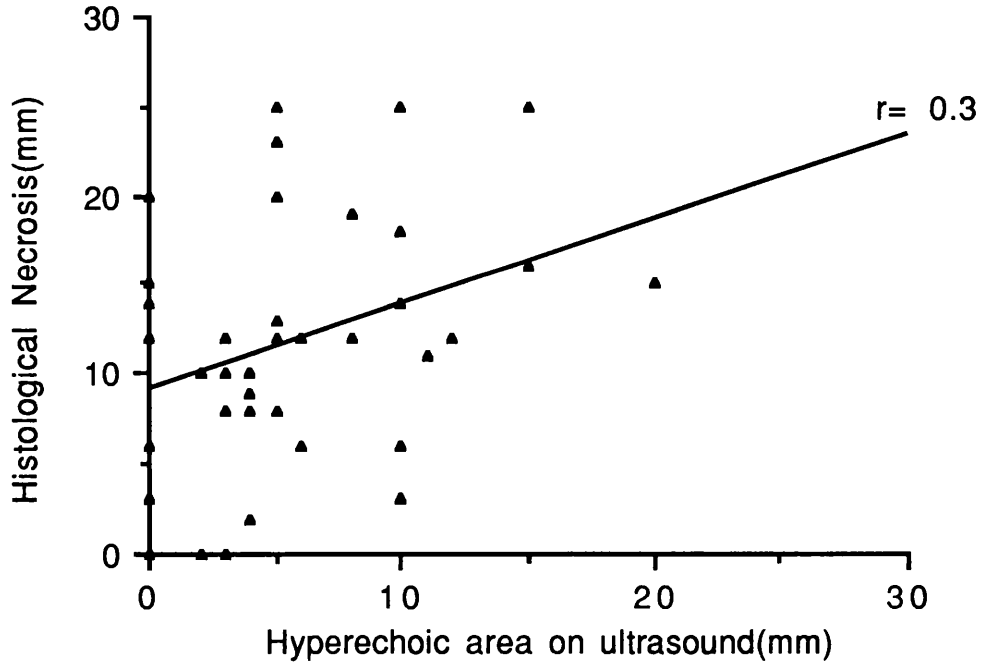


Figure 8.3: Ultrasound pictures seen a)before treatment b) during treatment(at 40 seconds) c) the hyperechoic area reached a peak at 490 seconds d)the area seen on ultrasound correlated poorly with the final histology when the tumour was resected 27 days after ILP and e) seen 3 minutes after the completion of ILP, the hyperechoic area having diminished in size.

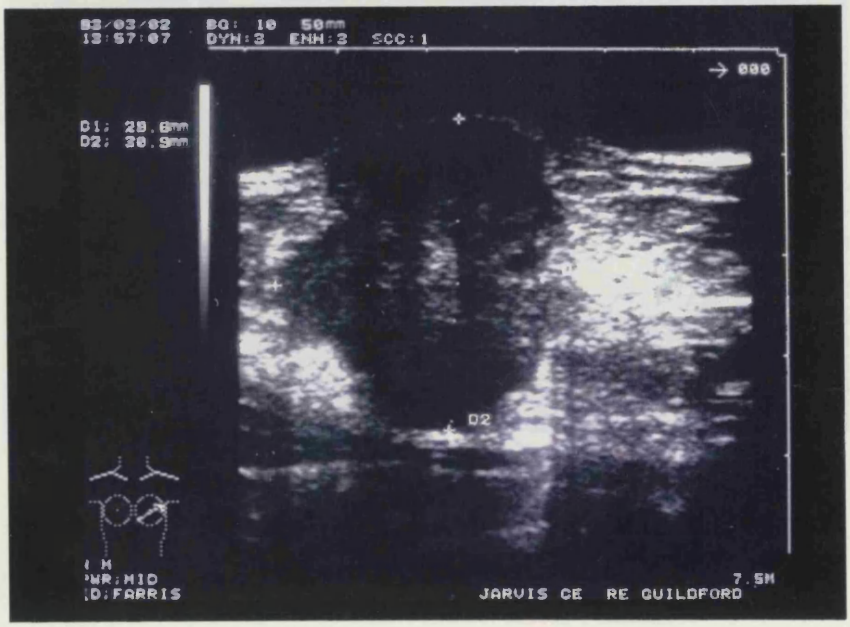


Figure 8.3a

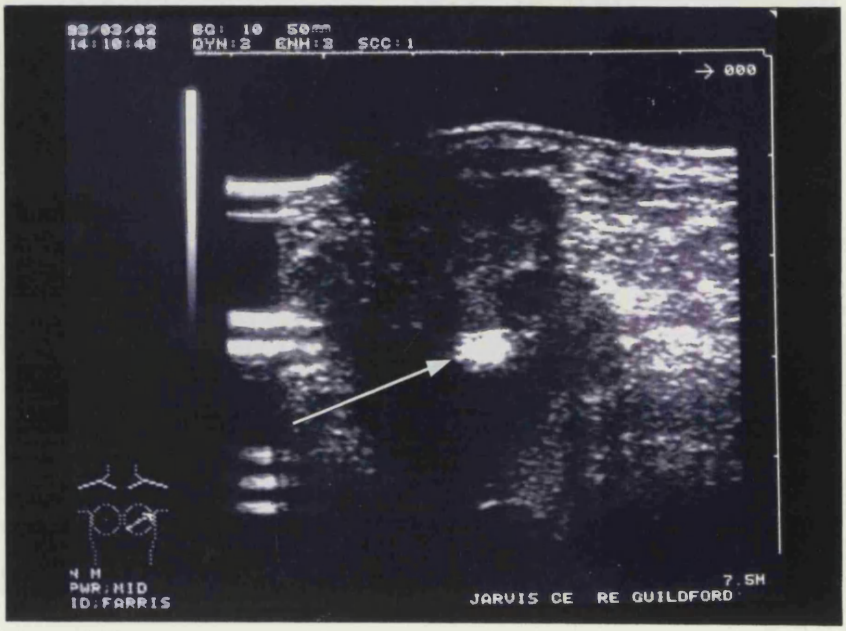


Figure 8.3b

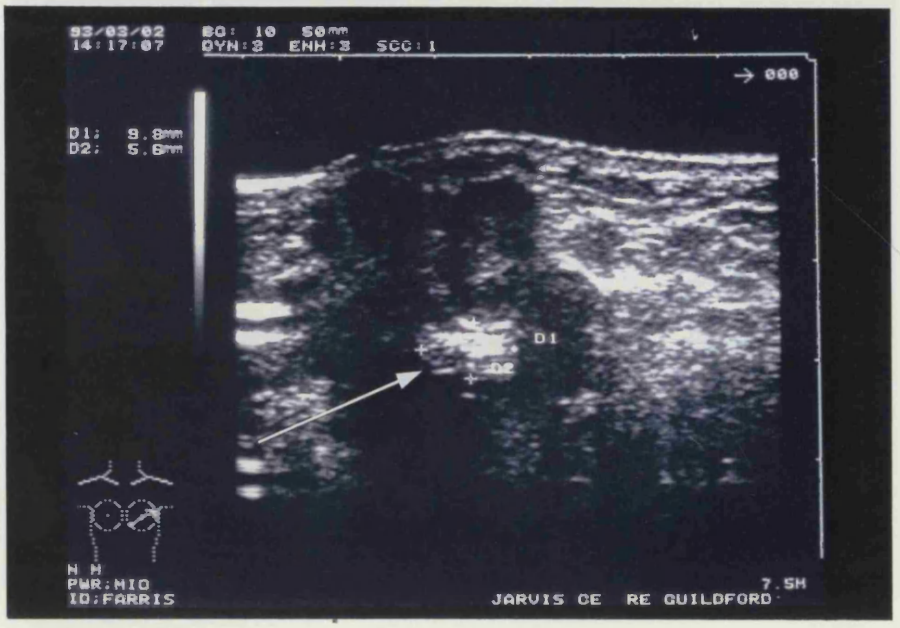


Figure 8.3c

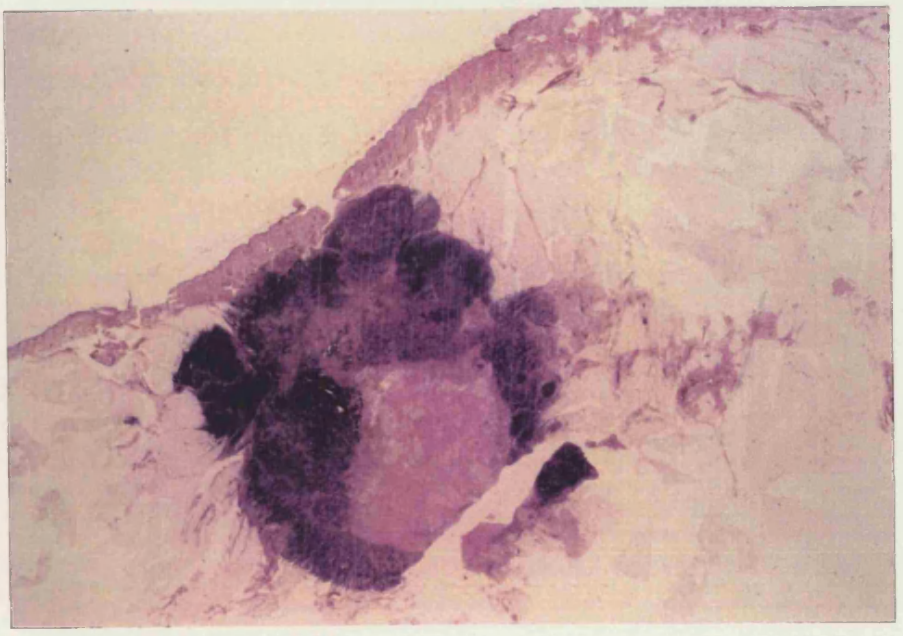


Figure 8.3d

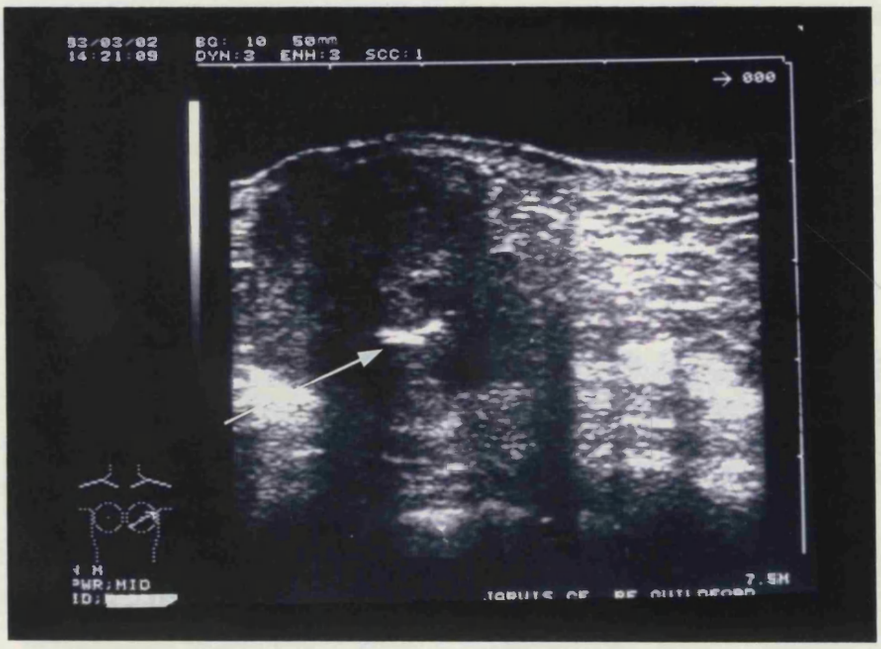
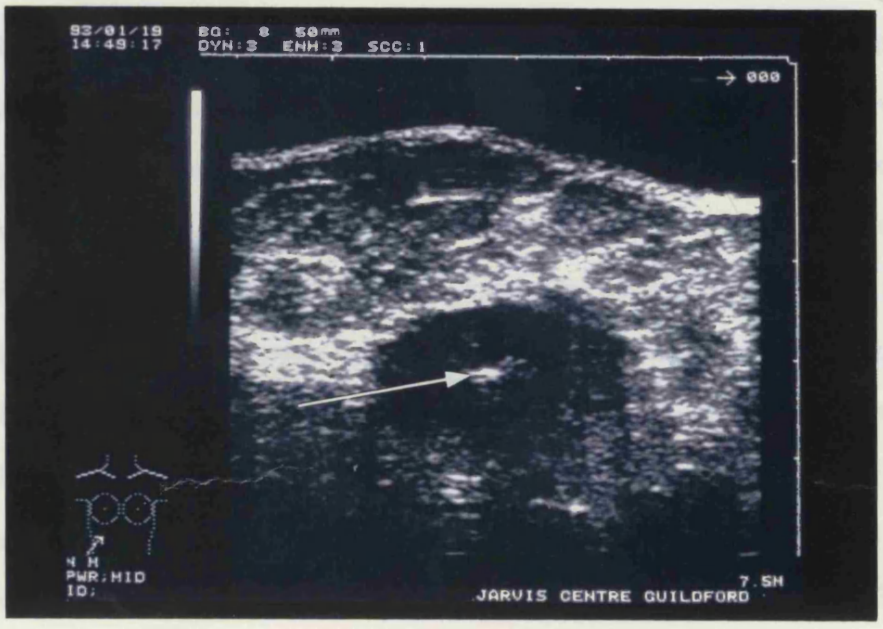
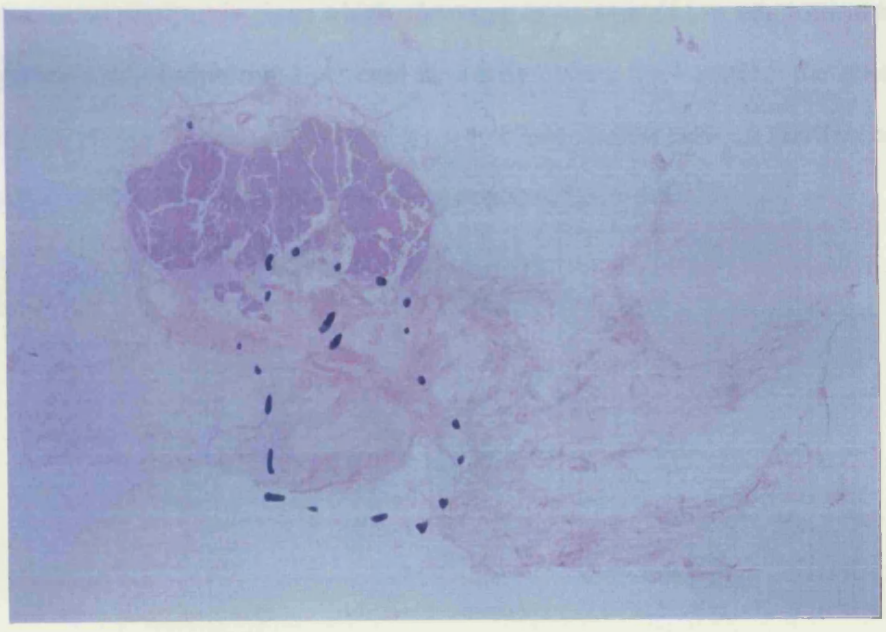


Figure 8.3e

Figure 8.4: Ultrasound underestimates the final diameter of necrosis, in this case(a papillary carcinoma) the maximum hyperechoic area was only 3mm(top and arrowed) and yet there was 25mm of necrosis in the final specimen(resected 6 days after ILP)which included some damage to surrounding normal breast tissue(bottom picture, the laser damage is within the area marked by the black ink) which was not visible on ultrasound.





8.2 Computerised Tomography (CT)Scanning

CT scanning was undertaken in 6 patients. Two in real time, 2 before and within 24 hours after ILP and a further 2 scans were performed 24 hours after ILP. The results are outlined in table 8.1. CT scans seen 24 hours after ILP are illustrated in figures 8.5 and 8.6 and scans seen in real time in figure 8.7.

Real time imaging requires intravenous contrast to image the tumour successfully as none of the tumours were clearly visible on CT without contrast. Of the two patients treated in real time in the CT scanner only one patient had demonstrable changes, which correlated with the histology but these were difficult to see. The other had no changes visible on CT as the laser fibre had passed through the back of the tumour and had caused thermal necrosis in the pectoralis major muscle, which was not evident on the CT scan either during treatment or immediately after treatment. Again, the real time imaging was difficult as there was considerable artefact at the tip of the needle(figure 8.7). Of the 4 patients who had CT scans post ILP, CT was accurate in assessing the diameter of necrosis within 4 mm in all patients. Following ILP not only is the tumour difficult to see but any necrosis produced by ILP is not evident unless intravenous contrast is given which shows up as an area of low attenuation surrounded by a high attenuation rim. In 1 case the cavity where (presumably) the laser fibre had passed(because it was surrounded by a low attenuation area on contrast scans) was visible on the post treatment CT without contrast(figure 8.6).

Table 8.1: CT results

Patient	Time relationship between ILP and CT scan.	Devascularisation on post ILP CT scan	Histological damage
1	Pre and 24 hrs post	Nil	Nil
2	Pre and 24 hrs post	8mm	10mm
3	24 hrs post	18mm	15mm
4	24 hrs post	15mm	11mm
5	Real time	5mm	6mm
6	Real time	Nil	8mm (in pectoralis major)

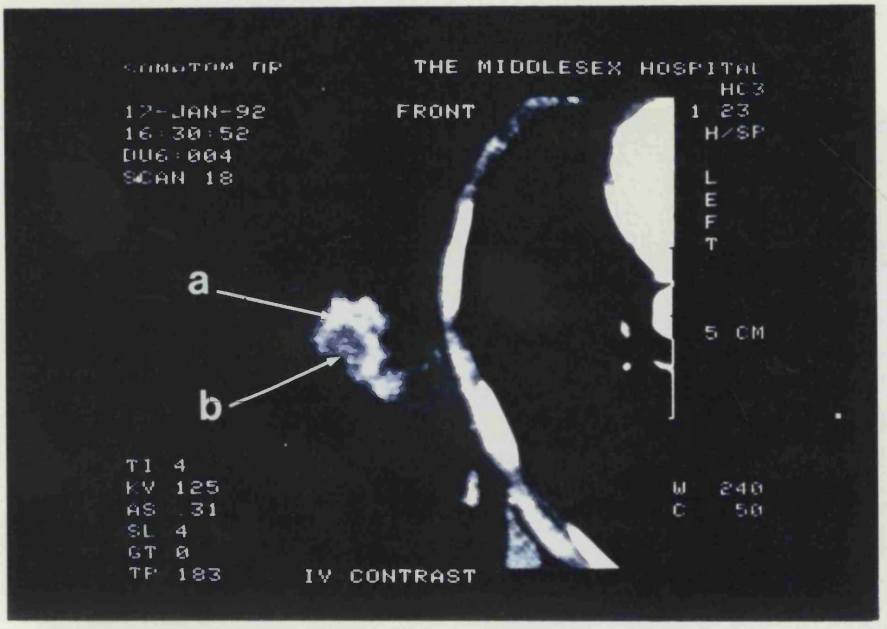


Figure 8.5: CT scan 24 hours after ILP. The tumour enhances (a) showing a devascularised area (b) which measures 15mm. The final diameter of necrosis measured 11mm histologically when resected 12 days after ILP.

Figure 8.6: CT scans seen 24 hours post ILP. 8.6a post laser pre-contrast 1=fibre tract 2= tumour and 8.6b post laser post contrast 1=fibre tract 2=tumour 3=laser induced necrosis.

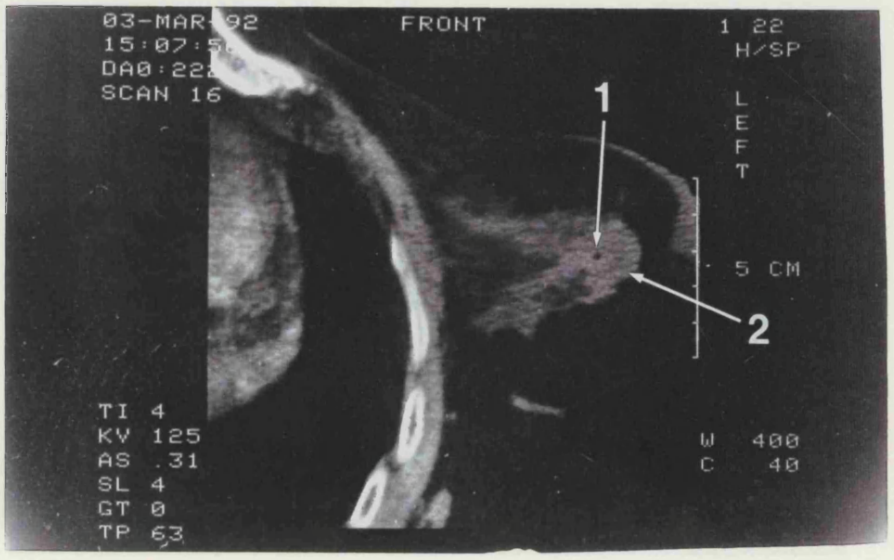


Figure 8.6a

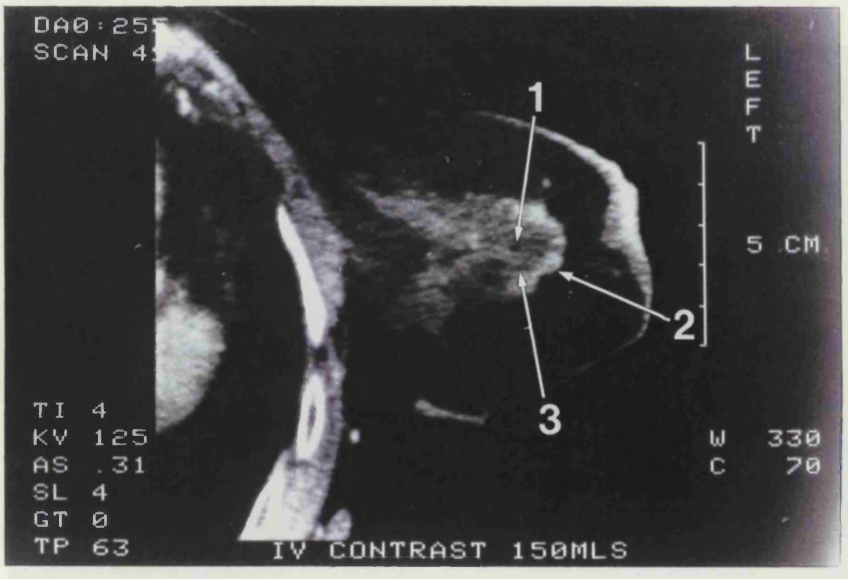


Figure 8.6b

Figure 8.7: CT scans seen in real time, no demonstrable changes were visible.a) pre laser post contrast(tumour arrowed) b)during ILP treatment needle(1) and tumour(2). Following treatment no changes were visible either in the tumour or surrounding tissue on CT scanning but 8mm of laser damage was subsequently found in pectoralis major.

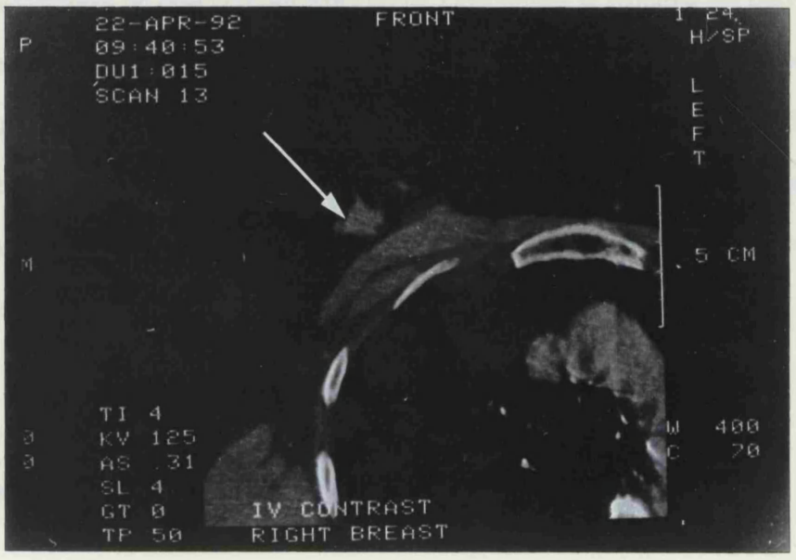


Figure 8.7a

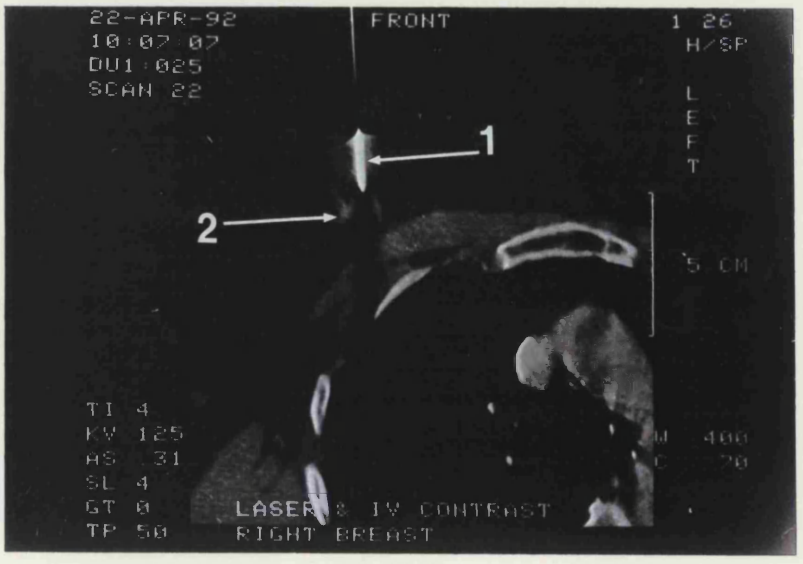


Figure 8.7b

8.3 Magnetic Resonance Imaging(MRI)

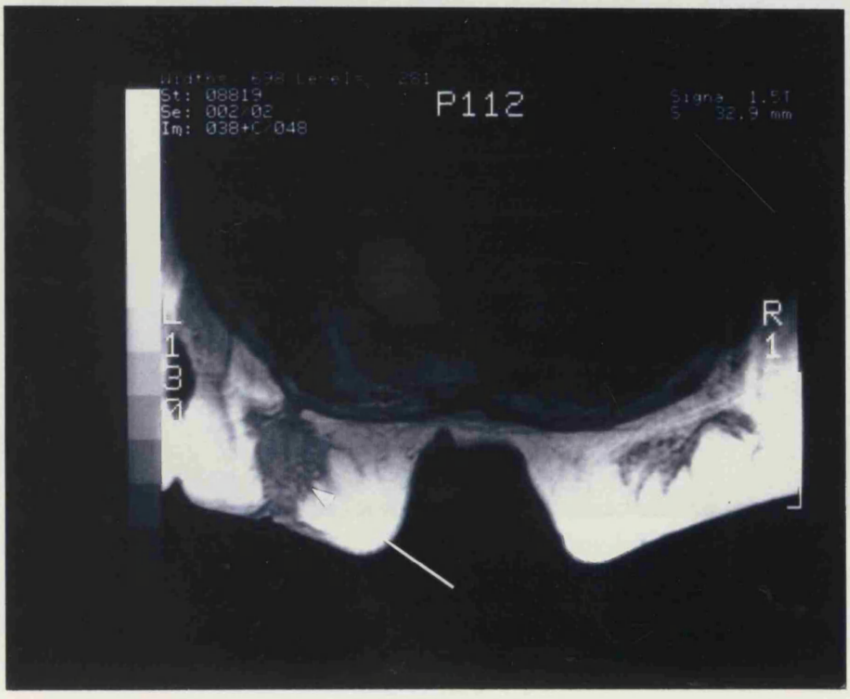
MRI was undertaken in 5 patients prior to and within 24 hours of ILP. Contrast enhanced T1 weighted sequences were performed with fat suppression. The results are shown in table 8.2. Laser induced necrosis was again seen as an area of reduced enhancement on post contrast MRI scans. Gadolinium is required not only to enhance the tumour but also to show the necrotic lesions(by the lack of enhancement). MRI scans are illustrated in figure 8.8 and 8.9. In five out of the 6 patients MRI correctly predicted the extent of necrosis within 4mm and predicted the extent of necrosis in the final patient within 6mm. Again in one patient the laser fibre tract was evident in the post laser pre-contrast scans.

Table 8.2 : MRI results

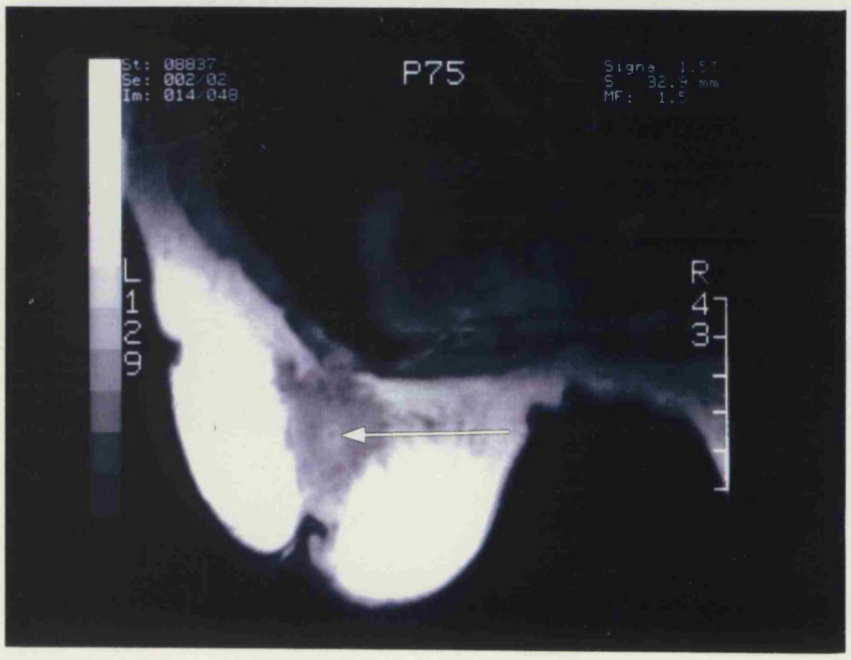
Patient	Time relationship between ILP and scan	Necrosis on MRI	Histological Necrosis
1	5 hrs post	15mm	16mm
2	5 hrs post	16mm	15mm
3	24 hrs post	12mm	12mm
4	24 hrs post	13mm	9mm
5	24 hrs post	18mm	12mm

Figure 8.8: MRI scans 24 hours post ILP(patient 3), a) pre-laser pre-contrast, the tumour is arrowed, b) post laser pre-contrast(laser fibre track arrowed) and c) Post laser post contrast an area of reduced enhancement is evident(arrowed) which corresponded exactly with the histology(d).

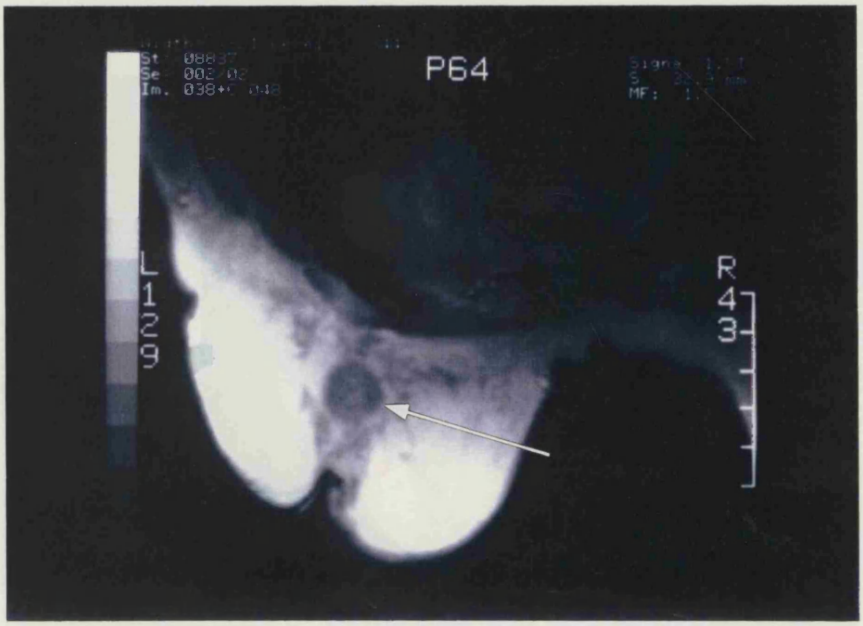
8.8a



8.8b



8.8c



8.8d

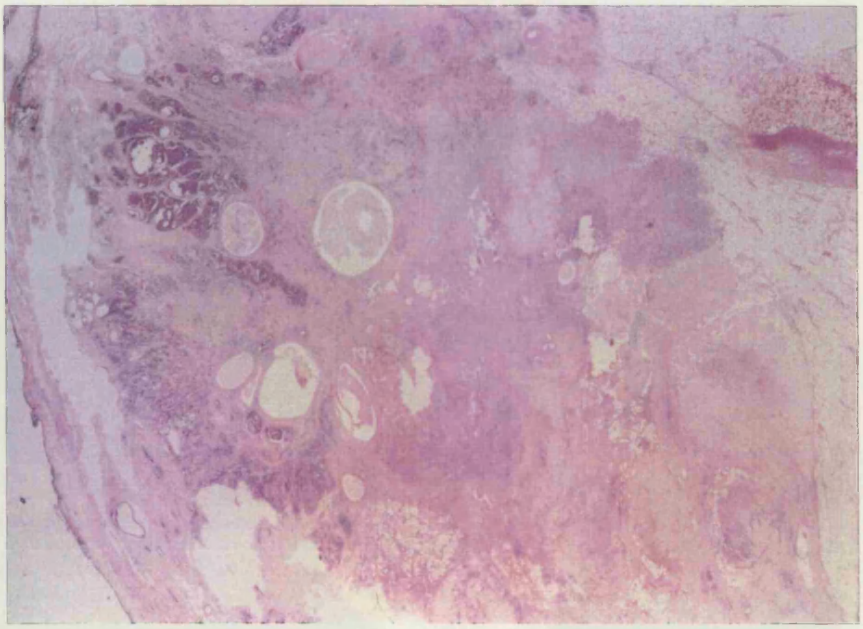
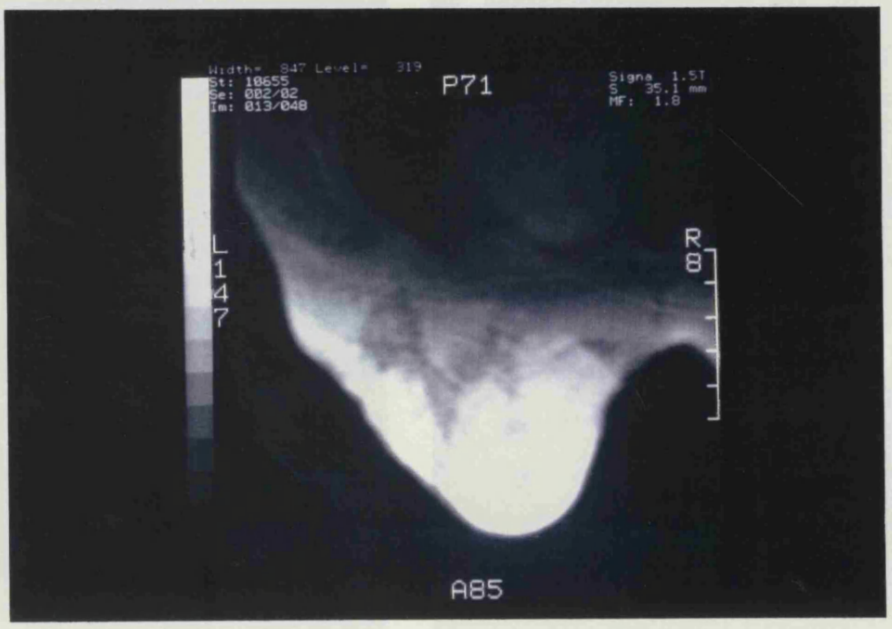
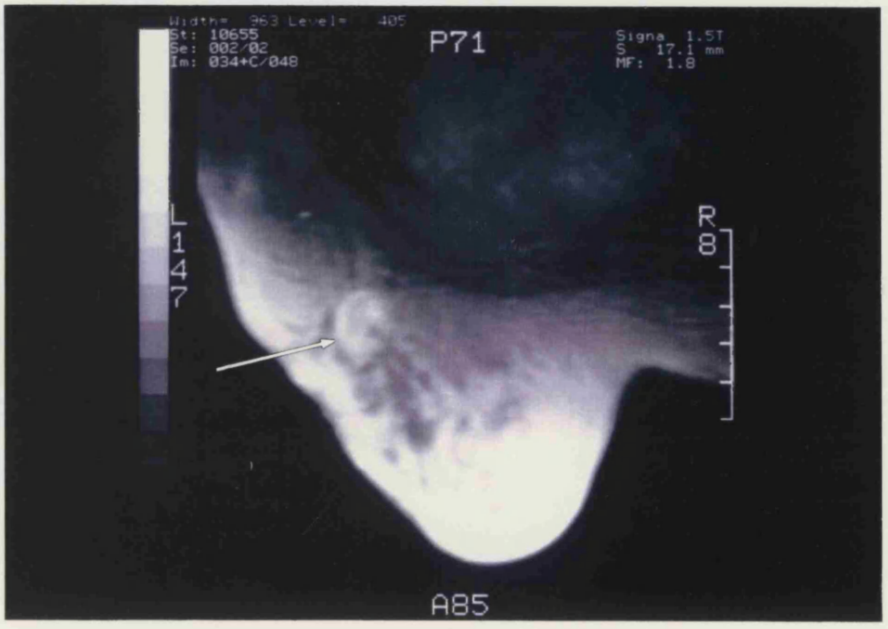


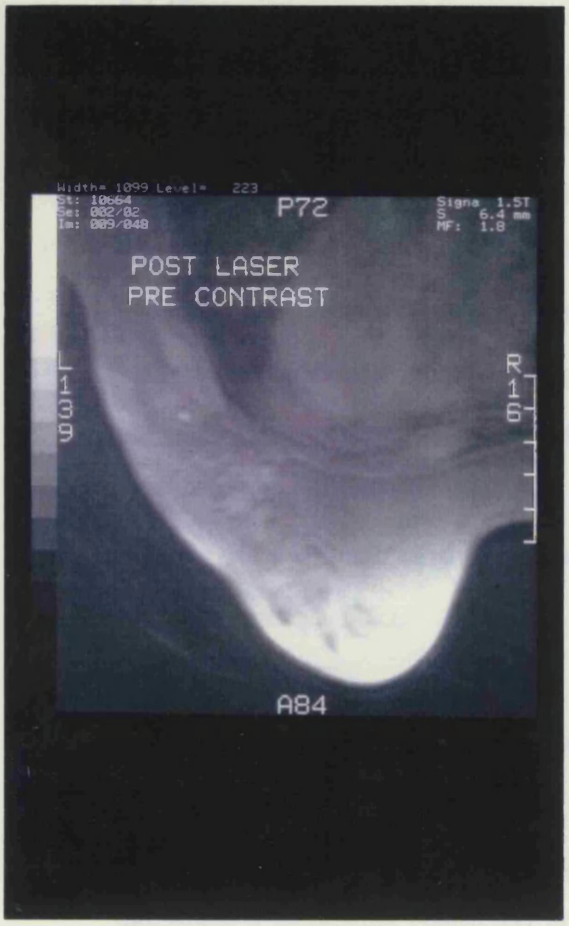
Figure 8.9: MRI scans a) pre laser pre-contrast b) pre-laser post contrast, the tumour enhances(arrowed) c) post laser pre-contrast and d) post laser post contrast



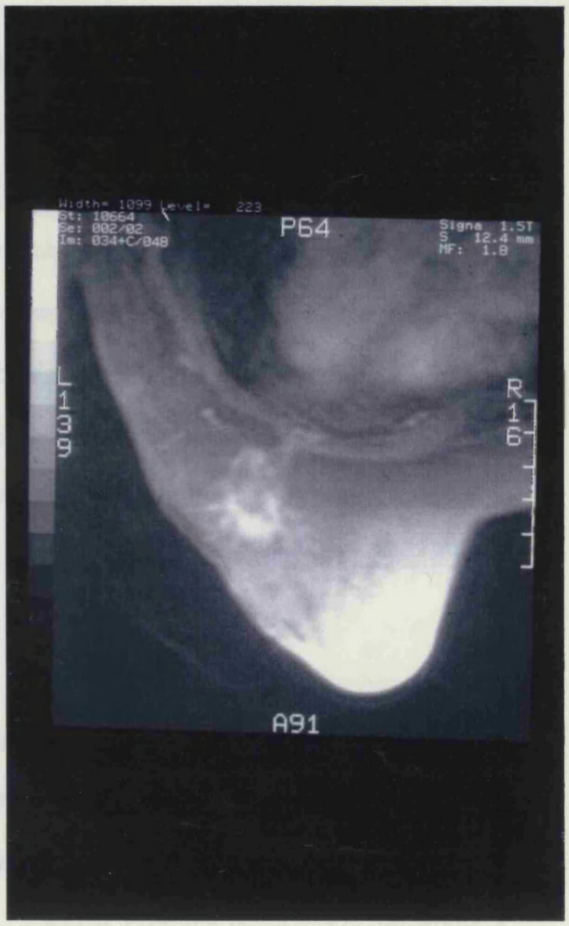
8.9a



8.9b


Width= 1099 Level= 223
St: 10664
Se: 002/02
Im: 089/048
P72
Signa 1.5T
S 6.4 mm
MF: 1.8
POST LASER
PRE CONTRAST
A84

8.9c


Width= 1099 Level= 223
St: 10664
Se: 002/02
Im: 034+C/048
P64
Signa 1.5T
S 12.4 mm
MF: 1.8
A91

8.9d

8.4 Discussion

If this technique is ever to become generally accepted then we must be able to satisfy ourselves that the tumour has been completely ablated during ILP and hence the search for an imaging technique that will allow accurate placement of the laser fibre within the tumour, accurately predict the boundaries of the tumour, allow real time monitoring of hyperthermic changes and predict the full extent of laser damage. We have undertaken some preliminary studies on the imaging required to monitor tumour ablation. We have not really explored the possibility of using mammography to monitor treatment mainly because in many patients who had pre-operative mammography and specimen radiography there was very little if any change in the appearance of the tumour following laser treatment.

The correlation between the size of the tumour seen on ultrasound and the size seen microscopically was reasonably good with a correlation coefficient of 0.6. Pain et al(1992) found ultrasound to underestimate tumour size as measured histologically describing a correlation coefficient of 0.75 whilst Fornage et al(1987) described a correlation coefficient of 0.84 with ultrasound tending to overestimate tumour size and the correlation between tumour size as measured by ultrasound and histology is the recent publication by Forouhi et al(1994) was good with a correlation coefficient of 0.89. These differences are accounted for by the fact that firstly, ultrasound is a very operator dependent procedure, secondly, it is difficult to be absolutely certain that the ultrasound measurements and the pathology measurements were taken in exactly the same planes and thirdly, tumours unlike benign lesions often have indistinct echogenic borders interfacing with the surrounding normal breast tissue often passing from a mixed echogenic area(mainly black) at the centre of the tumour to an indistinct 'fuzzy' border(grey) and it is difficult to know which side of this border to measure the tumour diameter from.

There was no correlation between the maximum diameter of thermal necrosis seen on ultrasound and that seen microscopically with ultrasound underestimating the extent of

necrosis in the majority of cases. It is difficult, again, to be certain that the ultrasound measurements and the pathology measurements were taken in the same plane. However, it is likely that the area of laser induced necrosis around the fibre tip is roughly spherical, so the diameter of necrosis will be approximately the same in all planes. The changes seen on ultrasound during ILP represent bubble formation in the tissues(from vapourization of tissue water) which disappear after the laser is switched off and coagulation and charring(changes which persist after cessation of the treatment) which probably do not extend to the full limits of the necrosed area. In experimental work Malone et al(1992) have also found ultrasound to be inaccurate in assessing the final extent of ILP induced necrosis whereas Dachman et al(1990), Bosman et al(1991) and Steger et al(1992)all found good correlation between ultrasound images and histology. It should be stressed that all these studies were performed in normal liver rather than in tumour tissue. The clinical work described by Amin et al(1993) used ultrasound to place the needles(and fibres) and to monitor ILP of hepatic metastases and found little correlation between the hyperechoic areas seen on ultrasound during ILP and the devascularised areas visible on dynamic CT scans 24 hours post ILP although correlation between images and histology was not possible as the tumours were not resected and no post mortems were performed. The hyperechoic areas were always visible at ultrasound during ILP of hepatic metastases and were often impressive in size but in some of our patients little in the way of hyperechoic areas were visible during ILP. Again, as mentioned above ultrasound is particularly operator dependent which may influence the results and explain the differences reported. It was however useful in placing the needle in the tumour although another imaging technique is needed to match the image with the extent of thermal necrosis seen microscopically. From the diagnostic point of view, colour doppler has shown promise(Cosgrove et al, 1993, McNicholas, M. et al, 1993) in predicting whether breast tumours are benign or malignant but has yet to be assessed in the imaging of laser tissue interactions.

CT scanning was only carried out in 6 patients and so meaningful conclusions cannot be drawn and the following statements must be interpretated with caution. It was

accurate in its estimation of the final diameter of necrosis in one of the 2 patients scanned at the time of treatment although it is known that CT is often not so useful immediately after ILP(Amin et al,1993d). In the patient in whom the laser fibre passed into the pectoralis major muscle no thermal changes were evident despite the fact that the area of necrosis was included in the CT field. The area of necrosis probably fell between cuts on the CT scan or alternatively could not be visualised immediately after treatment. This was only one case, but misplacement of the needle in pectoralis muscle did not occur in any patients when the needle was inserted under ultrasound guidance, suggesting that ultrasound is better from this point of view. In both patients treated with real time CT considerable artefact occurred at the tip of the needle making visualisation of thermal changes difficult although in future if CT were to be useful in assessing laser damage in real time it may be of use to insert the fibre and needle into the tumour and then withdraw the needle(making sure that the laser fibre does not move) and then taping the fibre to the skin to avoid any chance of skin burning. CT showed reasonable correlation with histology in the other four patients scanned at later times after treatment and certainly warrants further investigation although it is not convenient for repeated examinations because it is time consuming, requires fairly high doses of radiation and is relatively expensive. In addition, although all tumours in our series enhanced with iodonated contrast, other workers have found that reliable differentiation between benign and malignant tumours could not be achieved despite administration of intravenous contrast(Greenstein Orel and Troupin, 1993)

MRI of the breast probably has the greatest potential as a tool for diagnosing breast cancers as we have seen in chapter 1(1.2.5). The reported work by Kaiser et al(1993) and Harms et al(1993) stated sensitivities of 94-98%. Gadolinium is needed to enhance the tumour as in the series by Kaiser and Zeitler(1989) 20% of tumours showed up only after administration of gadolinium and the sensitivities have been improved by the use of fat suppression sequences. MRI has also been investigated as a potential tool for imaging ILP(chapter 4.8.4) and reasonable correlation between images and histology was recorded by Tracz et al(1993). In addition MRI is sensitive to alterations in water-

macromolecular interactions(Bottomley et al, 1984) and MRI can map tissue temperature changes(Jolesz et al,1988). Therefore combining the fact that MRI gives high sensitivities and can map temperature changes as well as monitor changes in tissue water content, MRI should be the imaging tool capable of fulfilling the criteria set for an ideal imaging technique. The number of patients who underwent MRI in our series was small and so again meaningful statements and conclusions cannot be drawn but of the five patients who underwent MRI scanning after ILP, MRI was accurate in three of these patients in predicting the final diameter of necrosis within 1mm but overestimated the extent of necrosis in the other two by 4 and 6mm. In our series it was necessary to give gadolinium as some of the tumours were not visible without contrast. The eventual dream would be to perform ILP in real time under MRI control possibly localising the tumour with the use of a stereotactic device currently under development(Hussman et al(1993). There are at present many barriers to overcome. Firstly, much further work is required to optimise the MR sequences, secondly MRI is at present expensive and not readily available and thirdly, it may be necessary in order to visualise the tumour and its boundaries to give gadolinium which in time could cause problems in visualising the tumour changes before and after treatment. The ILP times that we have used i.e. 500 seconds or so would mean that toward the end of real time ILP treatment the normal breast tissue surrounding the tumour will also enhance with gadolinium and the boundaries of the tumour would then be indistinct. The half life of gadolinium is approximately 90 minutes(M. Clemence, personal communication) and so after the tumour and then the surrounding normal breast tissue enhanced following injection of gadolinium repeat MR examination of the breast to assess the extent of ILP induced damage would not be possible for several hours. Work will also be needed to overcome this problem.

In the preceding work we have described the potential problems associated with ILP in that the laser treated area may heal with the formation of a hard fibrous area and differentiation between treated tumour, untreated tumour and local recurrence will be difficult. MRI has been put forward as a potential imaging device to differentiate these.

However some work reported recently(Cohen, 1993) has shown that MRI is unable to differentiate between scar tissue and local recurrence in the first 6 months after surgery because immature scar tissue will enhance with gadolinium. Whatever, MRI probably has the best potential to monitor the damage caused by ILP and is currently under intensive experimental and clinical evaluation in monitoring ILP.

CHAPTER 9: GENERAL DISCUSSION, CONCLUSIONS AND FUTURE RESEARCH

The introductory chapters in this thesis have documented the changes that have occurred in the treatment of breast cancer in the last 100 years or so. Moving away from treating breast cancer conservatively through the radical era and again into a conservative era where many prospective clinical trials with large numbers of patients and good statistical correlations have largely proved the safety and efficacy of breast conservation combined with radiotherapy as a safe alternative to mastectomy for selected patients. The survey of the management of breast cancer among surgeons in England and Wales has shown how conservative surgery is now a popular alternative to mastecomy with more surgeons advocating conservative surgery now than they did 10 years ago. The introductory chapter on interstitial laser photocoagulation(ILP) documented the available information on this new minimally invasive technique, its initial description in 1983, the early laboratory work and then the clinical work that followed. ILP could produce predictable areas of necrosis with safe healing and no general upset either to the animals or patients involved in this early work. The idea of ILP really takes the concept of conservative surgery for breast cancer a step further and the main question of this thesis was to ask whether it would be feasible to destroy breast cancers *in situ* utilising some form of imaging technique to accurately predict the extent of laser damage to ensure that the tumour and ideally a rim of normal breast tissue be destroyed with it.

Conservative surgery is a relatively easy and safe procedure to perform and in many cases a good cosmetic appearance can result. ILP would then have to have significant advantages over conservative surgery if it were to gain widespread acceptance and of course would have to prove that it had at least equal local control rates and overall survival to conventional surgery before it could be an accepted alternative to surgery. ILP would be easy to perform under local anaesthesia and should result in a better cosmetic result than surgery as no tissue is actually removed and there would be no obvious scarring. In addition, ILP could be performed as an outpatient and would be performed under some form of image guidance(possibly MRI)in real time. It may in theory(because it would ultimately be performed under image guidance where the

margins of the tumour would be easily visible) be more accurate in ensuring complete tumour destruction than surgery where even in the larger series(Fisher et al, 1985) 10% of patients have positive resection margins (a known risk factor for local recurrence which often necessitates further surgery in order to re-excise the tumour bed). It would be important therefore for ILP not only to destroy the tumour but also at least 1-2cms of adjacent normal breast tissue around the tumour.

Firstly, it would be worthwhile indicating which patients would be suitable for ILP if it were to become available. ILP could not be used to treat any cancer that had spread beyond the breast and any radiotherapy or chemotherapy required after surgery would also be required after ILP otherwise ILP would be associated with a high local failure rate. Although they have not been directly compared in a prospective trial, in theory, the indications and contraindications to use ILP would be the same as the indications to use conservative surgery at the present time(see chapter 2.1.3a), for example multifocal tumours and large tumours would be excluded. ILP probably would not be suitable for tumours which are impalpable and non-invasive on core biopsy for two reasons. Firstly, the treatment of a pure ductal carcinoma in situ(DCIS) is at present undetermined(the subject of a national prospective trial) and secondly if the core biopsy only showed DCIS it would not be possible to predict invasion elsewhere in the tumour. The results of ILP treatment of breast cancers have shown that ILP can produce predictable diameters of necrosis using a pre-charred fibre of 14mm. A necrotic diameter of 14mm would not really be of sufficient size to treat any tumours because it is necessary not only to destroy the tumour but a margin of normal breast tissue surrounding it, therefore, in order to treat the majority of tumours it would be neccesary to use the multiple fibre system as described by Steger et al(1992) and in current use in the treatment of hepatic metastases at our institution. The four fibre system is currently in operation with the Nd:YAG laser but a similar system is being developed for the diode laser.

If ILP were able to completely destroy breast cancers *in situ* one major disadvantage of the technique would be the loss of histological information. The current treatment of breast cancer is often based on the histological information gained following surgical resection of the tumour and will depend upon tumour type, grade, axillary nodal status and possibly upon the hormone receptor status and indices of proliferation. Adjuvant therapy (radiotherapy to chemo-endocrine treatment) can be instigated if necessary and patients can be placed into clinical trials in areas where uncertainty exists. It is therefore of the utmost importance that if ILP were to become available sufficient information be gained from the tumour prior to its ablation otherwise without a proper tissue diagnosis it would be difficult to prescribe appropriate adjuvant systemic chemotherapy leading to over treatment of some patients and under treatment of others. Equally, it may prove impossible to place patients appropriately into clinical trials without adequate histological details in areas where great uncertainty exists about patient management e.g. in the treatment of ductal carcinoma in situ. It would be inappropriate, for example, to prescribe chemotherapy to a patient with a 5mm, grade 1 node negative cancer which we can see from the overview of prognostic factors in chapter 3 has an excellent prognosis that does not differ from an age matched control without breast cancer(Todd et al,1987). It would be inadmissible also not to offer a premenopausal patient with a 3cm, grade 3 node positive tumour either appropriate chemotherapy or placement in an appropriate clinical trial. The alternatives available to procure histological information from a tumour prior to definitive treatment are fine needle aspiration cytology(FNAC) or core biopsy. FNAC is certainly an accurate tool capable of giving a definitive diagnosis of malignancy with specificity's of 99% and sensitivities of 87% reported(Fentiman, 1990). FNAC is not at present capable of distinguishing *in-situ* from invasive disease with any degree of accuracy although in some cases it can give an indication of tumour grade(Hunt et al,1990, Ciatto et al, 1993b), steroid hormone receptor status(Weintraub et al, 1987, Redard et al, 1989) and proliferative indices(Remvikos et al, 1991). For something like ILP where it would be necessary to procure not only a definitive diagnosis of malignancy but also be necessary to know the tumour type and grade before definitive treatment is instigated, FNAC would not

provide enough information. The alternative, also easy to do under local anaesthesia, is to perform a core biopsy which is capable of providing more information about tumour type and grade than FNAC. In the series from Baildam et al(1989) core biopsy correctly predicted tumour type in 93% of cases and in 69% of cases was able to correctly predict tumour grade. Core biopsy can also differentiate in situ from invasive cancer provided that invasive cancer is found in the core biopsy specimen, it cannot predict the presence of invasion when the core biopsy has only shown *in situ* changes and probably would not be able accurately to predict the presence of an extensive in-situ component within an invasive tumour(although there are no studies to support this statement), a known risk factor predictive for local recurrence within the breast. Core biopsy has a high sensitivity and a specificity of 100%(Fentiman, 1990). Careful studies will be needed to be sure that as much information can be obtained from this as from the whole resected tumour so that adjuvant therapy can be prescribed appropriately.

The technique appears to be safe with only two minor complications. One of a small bleed from the puncture site which was very easy to control and the second a skin burn caused by the laser fibre retracting during ILP and heating the shaft of the metal needle during the procedure. This later problem has now been overcome by taping the laser fibre to the needle during ILP to avoid this. Only 4 patients found the procedure frankly painful ; this could probably have been overcome by the use of intravenous sedation and analgesia and has not occurred in our most recent patients now that we have started to infiltrate under the tumour prior to ILP to prevent stimulation of the intercostal nerves which presumably caused the pain radiating to the axilla in 3 of the 4 patients. Creating a zone of necrosis within a tumour should in theory predispose the patient to develop an infection, although considering the high temperatures encountered possibly in the region of 300°C(Thomsen 1991) at the tip of the laser fibre it is unlikely that bacteria would be able to survive. No infections were seen in any of our patients. In theory, the creation of a necrotic area within a tumour may also stimulate the production of growth factors and angiogenic factors which could have a detrimental affect on prognosis. ILP certainly did not compromise survival in rat flank

fibrosarcomas(Mathewson et al, 1989) in fact, the survival in the ILP group was better than the surgical excision group and controls. We have seen no evidence that ILP has any detrimental effect on prognosis in any of our patients but the question can only be answered by careful, long term follow up. Only one patient in this series has died and that was from an unrelated disease and no loco-regional recurrences have occurred, although the longest follow up so far is only 26 months.

ILP is unlikely to be able to treat large tumours or obvious axillary disease but could possibly replace surgery as one aspect in the management of small breast cancers. It may be of value in the destruction of the small invasive breast cancers found in increasing frequency in the breast screening programme. This is only a preliminary study. We have shown that ILP of breast cancers is simple and safe and that zones of necrosis of about 1.5 cms in diameter can be produced around a single fibre and that the technique is more predictable if a pre-charred fibre is used. Ultrasound is convenient for the insertion of the fibre but is unable to predict the extent of laser damage, CT and MRI look promising for assessing the results of treatment but are at an early stage of development. Much further work is required to consolidate these results, particularly in refining the imaging to monitor therapy accurately in real time, but the technique of ILP does appear to have considerable promise as a potential therapeutic tool to destroy small breast cancers *in situ*.

If the technological problems outlined above can be overcome the proponents of ILP as a potential tool for treating breast cancer will be faced with setting up a randomised prospective controlled trial comparing conservative surgery and radiotherapy with ILP and radiotherapy. They would have to show that ILP was as effective as conventional surgery both in terms of local control and overall survival and in order to do that they would need to recruit large numbers of patients(possibly 1500-2000) and follow them up for at least 5 years. If the technological problems can be overcome and the results of the randomised trial showed that ILP was as effective as conventional surgery then ILP

could be a possible alternative to lumpectomy, but in reality this situation is very many years away.

Conclusions

The concept of using a minimally invasive treatment for breast cancer incorporates advances in the management of breast cancer, advances in lasers and advances in imaging. Conservative surgery has now been shown to be a safe alternative to mastectomy for selective patients, ILP has been shown to produce necrosis *in situ* with safe healing and imaging techniques such as MRI have increased the sensitivity of imaging for the detection of breast malignancy. The main thrust of this thesis is to enquire whether ILP could produce necrosis in breast cancers with safe healing and to ask if these changes can be visualised by some form of imaging technique.

We have shown that more surgeons would undertake conservative surgery than they have done in the past. We have also shown that charring was significantly associated with a larger diameter of necrosis but it is not possible to predict when charring will occur. However, by using a pre-charred fibre predictable diameters of necrosis can be produced in breast cancers with safe healing and few complications. Ultrasound was useful for placing the laser fibre within the tumour but was inaccurate at assessing laser damage. Dynamic CT and MRI have been investigated with only small numbers of patients but appear promising tools for delineating the areas of laser damage. Further studies are needed to optimise the imaging sequences before the technique is ultimately subjected to a clinical trial.

Future research

The main future thrust of research into ILP and breast cancer should focus on the imaging problems. Ultrasound has been shown to be ineffective and further studies need to be done to look at CT scanning especially with the newer spiral CT scanners. MRI also needs to be explored in many more patients. Firstly to optimise the sequences used, secondly to look at MR images at different times after ILP in order to assess at which time the images best approximate with histology and thirdly to start real time MRI imaging of ILP in the breast. The needle used would have to be non-magnetic and the needle and the fibre would probably be placed into the tumour under ultrasound control in a seperate room from the MR magnet. The use of long fibres means that the laser could be kept outside the MR room and it may be possible in the near future to utilise the stereotactic MR device described by Hussman et al(1993) and so real time MR imaging of ILP is really not far away.

The next move also may be to try to destroy the tumour completely using more than one fibre in the manner described by Steger et al(1992) and in current use in our ILP hepatic metastases programme and again utilise an imaging technique to predict the extent of laser damage. It would be important to have made sure that enough tissue has been taken from the tumour prior to ILP by means of a core biopsy.

Studies should also be done comparing the mean diameters of necrosis attained by using a pre-charred fibre with that attained by using the diffuser tip modification described by Nolsoe et al(1992). These studies need to be conducted initially in animal models possibly in normal rat or pig liver or alternatively in implantable flank tumours although the latter option is not so attractive because a proportion of these flank tumours become spontaneously necrotic when they are larger than 1cm in diameter. If the diffuser tip should prove superior to the pre-charred fibre then providing it will pass down the core of a 14G needle it could be then compared with the pre-charred fibre in human breast carcinomas. The other suggestions for future research would be to confirm that the differences in necrotic lesion diameter when using a clean fibre are due to differences in

the optical properties of breast cancers and differences in the optical properties within the same tumour. Although Key et al(1991) did study the optical properties of normal, glandular and malignant breast tumours the number of cancers studied was extremely small. Measurements of the optical properties of tissues is an area that this department has expertise in and it is relatively easy to measure optical properties of tumours. Another area that warrants confirmation is the area of in situ fixation that we have demonstrated in our tumours. Although this area has been shown to be non-viable in rat liver it would be relatively easy to show that this area was non-viable in breast tumours by use of NADPH diaphorase or bromodeoxyuridine staining techniques. The work contained in this thesis has been presented in many meetings in this country and overseas and one question that has been frequently raised is whether ILP has any detrimental effect on the patients prognosis, the basis for this question being the purely theoretical worries that ILP may cause release of angiogenic and growth factors. Again, in a suitable animal tumour model it should be possible to quantify the changes in growth factors and angiogenic factors that occur following ILP compared with a control population.

There is then a considerable amount of basic science and much further clinical work to be done to answer some of these complex questions that have arisen as a result of this thesis.

APPENDIX 1: Questionnaire from chapter 5(A)

ROYAL SURREY COUNTY HOSP.
GUILDFORD,
SURREY.

UNIVERSITY COLLEGE HOSP.
GOWER STREET,
LONDON WC1 6AU.

THE INVESTIGATION AND TREATMENT OF BREAST CANCER IN ENGLAND AND WALES IN 1992.

DEAR

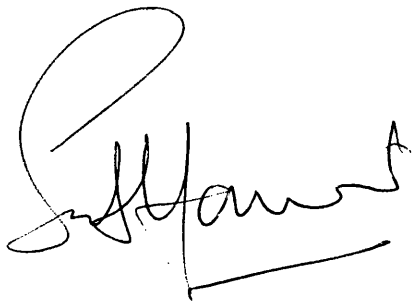
Breast cancer is a common condition presenting a large workload to general surgeons. The management of many aspects of breast cancer remains controversial,for example the treatment of the axilla by sampling or full dissection and in addition,there has been a move in the last 10yrs or so away from mastectomy toward more conservative surgery.

We enclose a short questionnaire which we have sent to 965 consultant surgeons in England and Wales outlining the management of the major areas of contention.

We would be very grateful if you could complete the questionnaire which takes less than 5 minutes to complete,please put a tick in the boxes provided and return it in the enclosed stamped addressed envelope.

Thank you for your cooperation.

YOURS SINCERELY,



MARK KISSIN Mchir,FRCS
CONSULTANT SURGEON

SIMON HARRIES,FRCS.
CLINICAL LECTURER.

I Would describe myself as a General Surgeon with an interest in .....

1. How is the workload of breast cancer distributed in your hospital ?

a) Managed largely by one consultant. ❑

b) Managed by more than one consultant. ❑

2. How many new cases of breast cancer do you see in your clinic annually?

Actual .....

Estimate .....

3. How many cases of breast cancer do you operate on annually?

Actual .....

Estimate .....

4. Do you have a regular combined breast meeting incorporating surgeons, radiologists,Oncologists etc?

YES	
NO	

INVESTIGATIONS

5. If a patient presented with a hard lump in the breast which of the following techniques would you routinely use to obtain a tissue diagnosis ?

a) Fine Needle Aspiration ❑

b) Tru-cut biopsy ❑

c) Excision biopsy. ❑

6. In staging a woman with breast cancer which of the following procedures would you perform ?

a) Bone scan ❑

b) Skeletal survey ❑

c) Liver Ultrasound ❑

d) Liver function tests ❑

e) Chest x-ray ❑

f) No staging procedures ❑

TREATMENT.

7. A woman with a large breast and a 2 cm. tumour in the upper outer quadrant proven by tru-cut biopsy to be a carcinoma I would treat by:

	Pre-Menopausal	*Post-Menopausal*
a) Tumourectomy		
b) Segmental Mastectomy or Quadrantectomy		
c) Mastectomy		

8. Regarding the treatment of her axilla I would:

	Pre-Menopausal	*Post-Menopausal*
a) Perform a full axillary dissection		
b) Perform a full axillary dissection only if the nodes were palpable		
c) Perform axillary sampling		
d) Perform axillary sampling only if the nodes were palpable		
e) Leave the axilla alone.		

9. An 82 yr. old otherwise fit lady with a 2cm. carcinoma in a moderate sized breast I would;

a) Treat with Tamoxifen ❑
b) Treat with Tamoxifen only if the oestrogen receptors were positive ❑
c) Recommend Lumpectomy ❑
d) Recommend Lumpectomy and Radiotherapy ❑
e) Recommend Lumpectomy and Tamoxifen ❑
f) Recommend Simple Mastectomy. ❑

10. A 62 yr. old lady who had a segmental mastectomy ,radiotherapy and Tamoxifen presents with a recurrence of her carcinoma at the site of her excision would you;

a) Treat by Mastectomy ❑
b) Treat by further wide excision ❑
c) Try another endocrine preparation such as medoxyprogesterone acetate ❑
d) Recommend Chemotherapy ❑

11. A 45yr old woman undergoes a Segmental Mastectomy, the histology shows a 2cm. carcinoma with tumour present at the resection margins would you;

a) Perform a further wide excision of the area ❑
b) Perform a mastectomy ❑
c) Refer for radiotherapy ❑
d) Refer for chemotherapy ❑

12. Do you have an input into the choice of chemotherapy given?

YES	
NO	

13.In what percentage of your breast cancer patients do you perform a mastectomy?

.....

FOLLOW UP.

14.Do you consider follow up of your breast cancer patients worthwhile?

YES	
NO	

If YES for how long? .....

15. Do you perform follow up investigations(e.g.bone scans,chest X-rays) on your breast cancer patients even if they are asymptomatic.

YES	
NO	

16. Following conservative treatment for breast cancer with lumpectomy and radiotherapy how often do you arrange follow up mammograms?

.....

PROJECT FUNDED BY FARMITALIA

REFERENCES

Allan, S., Rodger, A., Smyth, J. et al 1985 Tamoxifen as primary treatment of breast cancer in elderly or frail patients: a practical management.
BMJ 290:358

Amin, Z.(a) , Buonaccorsi, G., Mills, T. et al 1993 Interstitial laser photocoagulation: Evaluation of a 1320 Nd-YAG and an 805nm Diode laser: the significance of charring and the value of pre-charring the fibre tip.
Lasers Med Sci 8:113-120

Amin, Z.(b), Thurell,W., Spencer, G. et al CT pathologic assessment of laser induced necrosis in rat liver.
Invest. Radiol (in press)

Amin, Z.(c), Bown, S., Lees, W.R. 1993 Liver tumour ablation by interstitial laser photocoagulation: Review of experimental and clinical studies.
Seminars in Interventional Radiology 10(2):88-100

Amin, Z.(d), Donald, J.,Masters, A. et al 1993 Hepatic metastases:Interstitial laser photocoagulation with real time U/S monitoring and dynamic CT evaluation of treatment.
Radiology 187:339-347

Amin, Z.(e), Lees, W., Bown, S.G. 1993 Interstitial laser photocoagulation for the treatment of prostatic cancer.
Br J Radiol 66:1044-1047

Anon, 1953 Treatment of Breast Cancer.
BMJ 2:817-818.

Anon. 1985 Treatment of breast cancer-- is conservation safe ?
Lancet 1:964

Anscher, M., Jones, P., Prosnitz, L. et al 1993 Local failure and margin status in early stage breast carcinoma treated with conservation surgery and radiation therapy.
Ann Surg 218(1):22-28

Anzai,Y., Lufkin, R., Hirschowitz, S. et al 1992 MR imaging-histopathologic correlation of thermal injuries induced with interstitial Nd:YAG laser irradiation in the chronic model.
JMRI 2:671-678

Atkins, H., Hayward, J.L., Klugman, D.J. et al 1972 Treatment of early breast cancer: A report after ten years of a clinical trial.
BMJ 2:423-429

Badwe, R.,Gregory,W.,Chaudray, M.et al, 1991 Timing of surgery during menstrual cycle and survival of premenopausal women with operable breast cancer.
Lancet 337:1261-1264.

Baildam, A., Turnbull, L.,Howell, A. et al 1989 Extended role for needle biopsy in the management of carcinoma of the breast.
Br J Surg 76:553-55\8

Barnes, D.M., Lammie, G.A., Millis, R.R. et al 1988 An immunohistochemical evaluation of c-erb B2 expression in human breast cancer.
Br J Cancer 58:448-452

Barraclough, J., Pinder, P.,Cruddas, M. et al 1992 Life events and breast cancer prognosis.
BMJ 304:1078-81.

Bartelink, H., Borger, J., van Donegan, D et al 1988 The impact of tumour size and histology on local control after breast conserving therapy.
Radiother Oncol 11:297-303

Basnett, I., Gill, M., Tobias, J.S. 1992 The management of breast cancer in a teaching and a non-teaching district.
Eur. J. Cancer 28A (12);1945-50 .

Bates, T., Riley, D., Houghton, J et al 1991 Breast cancer in elderly women: a cancer research campaign trial comparing tamoxifen alone with tamoxifen and optimal surgery.
Br J Surg 78:898-900

Bates, T., Riley , D., Houghton, J. et al 1992 Tamoxifen treatment for breast cancer in elderly patients.
Br J Surg 79:454(Abstract)

Blanc, D., Colles, M. 1990 Transmission measurements on various tissue samples between 1064 and 2000nm
Lasers Med Sci 5:71-75

Bleehen, N.M. 1982 Hyperthermia in the treatment of cancer.
Br J Cancer supp.4596-100

Bloom, H., Richardson,W. 1957 Histologic grading and prognosis in breast cancer.

Br J Cancer 11:359-377.

Bloom, H., Richardson, W., Harries, E. 1962 Natural history of untreated breast cancer (1805-1933)
BMJ 2:213-220.

Bonadonna, G., Valagussa, P., Brambilla, C. et al 1991 Adjuvant and neo-adjuvant treatment of breast cancer with chemotherapy and/or endocrine therapy.
Sem Oncol 18:515-524

Bosman, S., Phoa, S., Bosma,A. et al. 1991 Effects of percutaneous interstitial thermal laser on normal liver of pigs: sonographic and histopathological correlations.
Br J Surg 78:572-575

Bottomley, P., Foster, T., Argersinger, R. 1984 A review of normal tissue hydrogen NMR relaxation times and relaxation mechanisms from 1-100 MHz: Dependency on tissue type, NMR frequency, temperature, species, excision and age.
Med Phy 11:425-448

Bown, S.G.1983 Phototherapy of tumours
World J Surgery 7:700-709

Boyd,N.,Campbell,J.,Germanson,T. et al 1981 Body weight and prognosis in breast cancer.
JNCI 67:785-789.

Brackett, K., Sankar, M., Joffe, S. 1986 Effects of Nd-YAG laser photoradiation on intra-abdominal tissues: A histological study of tissue damage versus power density applied.
Lasers Surg Med 6:123-130

Bradbeer,J., Kyngdon, J. 1983 Primary treatment of breast cancer in elderly women with tamoxifen.
Clin Oncol 9:31-34

Breasted, J.H. : The Edwin Smith Surgical Papyrus Volume 1. University of Chicago,1930.

Bucalossi, P.,Veronesi,V., Zingo,L. et al 1971 Enlarged mastectomy for breast cancer: A review of 1213 cases.
Am.J.Roentgenol. Radium Ther.Nucl. Med. 11:119-122.

Busch,W. *Verh Naturh Ver Preuss Rheinl,1866:23;28*

Carter, C., Allen, C., Henson, D.1989 Relation of tumour size, lymph node status, and survival in 24,740 breast cancer cases.
Cancer 63:181-187.

Castren-Persons, M. Lipasti, J., Puolakkainen, P. et al 1992 Laser induced hyperthermia: Comparison of two different methods
Lasers Surg Med 12:665-668

Chamberlain, J. Epidemiology of breast cancer in Breast Cancer(U.I.C.C.) editors
I.Burn and H.J.G. Bloom, Publ:Springer Verlag.1989.

Chauvet, B., Reynaud-Bougnoux, A., Calais, G. et al 1990 Prognostic significance of breast relapse after conservative treatment in node negative early breast cancer.
Int J Radiat Oncol Biol Phys 19:1125-1130

Chouillet, A., Bell, C., Hiscox, J. 1994 Management of breast cancer in South-East England.
BMJ 304:168-71

Ciatto, S., Cariaggi, P., Bulgaresi, P. et al 1993 Fine needle aspiration cytology of the breast: a review of 9533 consecutive cases.
Breast 2:87-90 (a)

Ciatto, S., Bonardi, R., Herd-Smith, A. et al 1993 Prognostic value of breast cancer cytologic grading.
Diagn Cytopathol 9(2):160-163 (b)

Clarke, D., Le' , M., Sarrazin, D. et al 1985 Analysis of local regional relapse in patients with early breast cancers treated by excision and radiotherapy: Experience of the Instit- Gustave Roussy.
Int J Radiat Oncol Biol Phys 11:137-145

Clayton, F.1986 Pure mucinous carcinomas of the breast: morphologic features and prognostic correlates.
Hum Path 17:34-39

Clemente, C.,Boracchi, P.,Andreola, S .et al 1992 Peritumoral lymphatic invasion in patients with node- negative mammary duct carcinoma.
Cancer 69:1396-1403.

Cohen, E. 1993 Current status of MRI.
Toronto breast imaging(abstract) 1:51-55

Coley,W.B.1893 The treatment of malignant tumours by repeated inoculations of erysipelas : with a report of ten original cases.

American Journal Of Science 105;487-511

Cosgrove, D.,Kedar, R.,Bamber, J. et al 1993 Breast diseases:Colour doppler US in differential diagnosis.
Radiology 189:99-104

Crowe,J.P.,Gordon,N.,Shenk,R.et al 1992 Primary tumor size, Relevance to breast cancer survival.
Arch Surg 127:910-916.

Dachman, A.,McGhee, J.,Beam, T., et al 1990 US guided percutaneous laser ablation of liver tissue in a chronic pig model.
Radiology, 176:129-133.

Dachman, A., Smith, M., Burris, J. et al 1992 Interstitial tumour ablation using Nd:YAG laser in a VX2 carcinoma model.
Lasers Surg Med 12:130(Abstract)

Daikuzono, N., Suzuki, S.,Tajiri, H. et al 1988 Laserthermia, a new computer controlled contact Nd:YAG system for interstitial local hyperthermia.
Lasers Surg Med 8:254

Daikuzono, N., Joffe, S. 1985 Artificial sapphire probe for contact photocoagulation and tissue vapourisation with the Nd:YAG laser.
Med Instrum 19:173-178

Davis, B., Gelber, R., Goldhirsch, A. et al 1986 Prognostic significance of tumour grade in clinical trials of adjuvant therapy for breast cancer with axillary lymph node metastases.
Cancer 58:2662-2670.

De Waard, F.Poortman, J.,Collette, B. 1981 Relationship of weight to the promotion of breast cancer after menopause.
Nutr.Cancer 2:237-240.

DeWys, W. 1972 Studies correlating the growth rate of a tumour and its metastases and providing evidence for tumour related systemic growth retarding factors.
Cancer Res 32:1488-1492

Dixon, A., Ellis, I., Elston, C.et al, 1991 A comparison of the clinical metastatic patterns of invasive lobular and ductal carcinomas of the breast.
Br J Cancer 63:634-635.

Dixon, J., Anderson, T., Page, D. et al 1982 Infiltrating lobular carcinoma of thebreast.
Histopathology 6:149-161.

Dixon, J., Chetty,U. 1991 Mammography in the management of patients with small breast cancer
Br J Surg 78:218-219

Dixon, J. 1992 Treatment of elderly patients with breast cancer.
BMJ 304:997-998

Dowlatshahi, K., Babich, D., Bangert, J. et al 1992 Histologic evaluation of rat mammary tumour necrosis by interstitial Nd-YAG laser hyperthermia.
Lasers Surg Med 12:159-164

Early Breast Cancer Trialists Collaborative Group. 1992 Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy: 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women.
Lancet 339:1-15,71-85.

Egan, R. 1960 Experience with mammography in a tumour institute. Evaluation of 1000 studies.
Radiology 75:894-900

Elledge, R., McGuire, W., Osborne, C.K. 1992 Prognostic factors in breast cancer.
Semin Oncol 9(3):244-253.

Ellis, I.O., Galea, M., Broughton, N. et al 1992 Pathological prognostic factors inbreast cancer II. Histological type. Relationship with survival in a large study with long follow up.
Histopathology 20:479-489.

Essenpreis, M.,Van der see, P., Mills, T.N. 1991 Monte Carlo modelling of light transmission in tissue; Effect of laser coagulation on light distribution.
SPIE Proceedings 1524:122-137

Fallowfield, L.J., Baum, M., Maguire, G.P. 1986 Effects of breast conservation on psychological morbidity associated with the diagnosis and treatment of early breast cancer.
BMJ 293:1331-1334

Fentiman, I., Lavelle, M., Kaplan, D.et al 1986 The significance of supraclavicular fossa node recurrence after radical mastectomy.
Cancer 57:908-910.

Fentiman I., 1990, *Detection and treatment of early breast cancer*. London: Martin Dunitz :193-206.

Fentiman, I.S., Mansel, R.E. 1991 The axilla: Not a no go zone
Lancet 337;221-3.

Fessenden, P., Lee, E., Samulski, T. 1984 Direct temperature measurements.
Cancer Res 44(suppl): 4799-4804

Fisher, B., Slack, N., Katrych, D. et al 1975 Ten year follow up results of patients with carcinoma of the breast in a cooperative clinical trial evaluating surgical adjuvant chemotherapy.
Surg Gynaecol Obstet 140:528-534.

Fisher, B., Bauer, M., Margolese, R. et al 1985 Five year results of a randomised clinicaltrial comparing total mastectomy and segmental mastectomy with or without radiation in the treatment of breast cancer.
N Engl J Med 312:665-673

Fisher, B., Redmond, C., Poisson, R. et al 1989 Eight year results of a randomised clinical trial comparing total mastectomy and segmental mastectomy with or without radiation in the treatment of breast cancer.
N Engl J Med 320:822-828

Fisher, B., Anderson, S., Fisher, E. et al 1991 Significance of ipsilateral breast tumour recurrence after lumpectomy
Lancet 338:327-31

Fisher, B., Costantino, J., Redmond,C. et al 1993 Lumpectomy compared with lumpectomy and radiation therapy for the treatment of intraductal breast cancer.
N Engl J Med 328:1581-1586

Fisher, E., Sass, R., Fisher, B. et al 1986 Pathologic findings from the National Surgical Adjuvant Breast Project.
Cancer 57:1717-1724

Foekens, J., Rio, M., Seguin, P et al 1990 Prediction of relapse and survival in breast cancer patients by ps2 protein status.
Cancer Res. 50:3832-3837

Fornage, B., Toubas, O., Morel, M. 1987 Clinical, mammographic and sonographic determination of pre-operative breast cancer size.
Cancer 60:765-771

Forouhi, P.,Walsh, J., Anderson, T., Chetty, U. 1994 Ultrasonography in the management of breast cancer.
Br.J.Surg 81:223-225

Fourquet, A., Campana, F., Zafrani,B. et al 1989 Prognostic factors of early breast recurrence in the conservative management of early breast cancer: a 25 year follow up.
Int J Radiat Oncol Biol Phys 17:719-725

Frazier, T., Wong, R., Rose, D 1989 Implications of accurate pathologic margins in the treatment of primary breast cancer.
Arch Surg 1989;124:37-38

Gazet, J.C., Rainsbury, R.M., Ford, H.T. et al 1985 Survey of treatment of primary breast cancer in Great Britain.
BMJ 290:1793-5.

Gazet, J.C., Markopoulos, C., Ford, H. et al 1988 Prospective randomised trial of tamoxifen versus surgery in elderly patients with breast cancer.
Lancet i:1679-1681

Gelber, R., Goldhirsh, A., 1989 Menstrual effect on surgical cure of breast cancer.
Lancet ii:1344

Ghossein, N., Alpert, S., Barba, J. et al 1992 Importance of adequate surgical excision prior to radiotherapy in the local control of breast cancer in patients treated conservatively.
Arch Surg 127:411-415

Gilchrist, K., Kalish, L., Gould,V.et al 1985 Inter-observer reproducibility of histopathological features in stage II breast cancer.
Breast Cancer Res. Treat. 5:3-10.

Greenstein Orel, S., Troupin, R. 1993 Non-mammographic imaging of the breast: Current issues and future prospects.
Semin Roentgenol 28:231-241

Greenway, B. 1988 Hepatic metastases from colorectal cancer:resection or not.
Br J Surg 75:513

Haagenson, C, 1986 *Diseases of the Breast*, 3rd ed, p656,Philadelphia,W. B. Saunders

Haagenson, C. 1977 Treatment of curable carcinoma of the breast.
Int J Radiat Oncol. Biol Phys 2:975-980.

Hallahan, D., Michel, A., Halpern, H. et al 1989 Breast conserving surgery and definitive irradiation for early stage breast cancer.
Int J Radiat Oncol Biol Phys 17:1211-1216

Halsted, W.S. 1894 The results of operations for the cure of cancer of the breast performed at the John Hopkins Hospital from June 1889 to January 1894.
Arch. Surg 20:497-501.

Halsted,W., 1907 The results of radical operations for the cure of cancer of the breast .
Ann Surg 46:1-19

Harms,S., Flamig,D.,Hesley,K et al 1993 MR imaging of the breast with rotating delivery of excitation off resonance: Clinical experience with pathologic correlation.
Radiology 187:493-501

Harries, S.A., Scrivener, R., Lawrence, R.N. et al. 1993 Regional variations in the surgical treatment of early breast cancer.
Br J Surg 80(6):809

Harris, J., Hellman, S., Henderson, I.C., Kinne, D. 1991: *Breast Diseases,* Published by J.B.Lippincott.

Harris, M., Howell, A., Chrissohou, M.et al 1984 A comparison of the metastatic pattern of infiltrating duct carcinoma of the breast.
Br J Cancer 50:23

Hashimoto, D., Takami, M., Ideezuki, Y. 1985 In depth radiation therapy by Nd-YAG laser for malignant tumours of the liver under ultrasonic imaging.
Gastroenterology 88: A1663

Haybittle, J.,Blamey, R., Elston, C. et al 1982 A prognostic index in primary breast cancer.
Br J Cancer 45:361

Hayward, J.L. Trials of wide excision and radiation therapy at the Breast Unit, Guy's Hospital, London. In: Zander J.B. *Early breast cancer.* (Springer-Verlag: Berlin, Heidelberg 1985)

Hayward, J.L., Caleffi, M. 1987 The significance of local control in the primary treatment of breast cancer.
Arch Surg 122:1244-1247

Henderson, I.1990 The treatment of metastatic breast cancer with adjuvant systemic therapy.
Annals Oncol :9-11.

Higuchi, N, Bleier, A., Jolesz,F. et al 1992 MRI of the acute effects of interstitial laser irradiation on tissues.
Invest Radiol 27:814-821

Hillernen, D., Anderson, I., Lindholm, K. et al 1991 Invasive lobular carcinoma: mammographic findings in a 10 year experience.
Radiology 178(1):149-154

Holland, R., Connolly, J , Gelman, R. et al 1990 The presence of an extensive intraductal component following a limited excision correlates with prominent residual

disease in the remainder of the breast.
J Clin Oncol 8:113-118

Host, H., Lund, E. 1986 Age as a prognostic factor in breast cancer.
Cancer 57:2217-2221.

Howell, A., Barnes, D., Harland, R.. et al 1984 Steroid hormone receptors and survival after first relapse in breast cancer.
Lancet 1:588

Hrushesky, W., Bluming, A., Gruber, S.et al. 1989 Menstrual influence on surgical cure of breast cancer.
Lancet i:949-52.

Hunt, C., Ellis, I., Elston, C. et al 1990 Cytological grading of breast carcinoma- a feasible proposition?
Cytopathology 1990;1:287-295

Hussman, K., Renslo, R., Phillips, J. et al 1993 MR mammographic localisation.
Radiology 189:915-917

International (Ludwig) Breast Cancer Study Group., 1990 Prognostic importance of occult axillary lymph node metastases from breast cancers.
Lancet 335:1565-1568.

Jacquemier, J., Kurtz, J.M., Amalric, R. et al 1990 An assessment of extensive intraductal component as a risk factor for local recurrence after breast conserving therapy.
Br J Cancer 61:873-876

Jacques, S., Rastegar, S., Mostamedi, M.et al 1992 Liver photocoagulation with diode(805nm) versus Nd:YAG laser(1064nm)
SPIE proceedings,laser tissue interactions III,1646

Jolesz, F., Bleier, A., Jakab, P. et al 1988 MR imaging of laser tissue interactions.
Radiology 168:249-253

Kaiser,W., Zeitler, E. 1989 MR imaging of the breast: Fast imaging sequences with and without Gd-DTPA
Radiology 170:681-686

Kaiser, W. 1993 MR mammography(MRM) Berlin, Germany:Springer-Verlag 21-88

Karanov, S., Karaivanova, M, Karanova, S. et al 1992 External beam, sapphire tip contact and interstitial Nd-YAG laser therapy at 1.064μm on a transplanted adenocarcinoma in mice: A comparative study.
Lasers Med Sci 7:483-486

Key, H., Davies, E., Jackson, P. et al 1991 Optical attenuation characteristics of breast tissues at visible and near infra-red wavelengths.
Phys Med Biol 36:579-590

Keynes, G. 1937 Conservative treatment of cancer of the breast.
BMJ 2:643-647.

Krecke, K., Gisvold,J. Invasive lobular carcinoma of the breast: Mammographic findings and extent of disease at diagnosis in 184 patients.
AJR 1993;161:957-960

Kurtz, J. , Amalric,R., Brandone, H. et al 1989 Local recurrence after breast conserving surgery and radiotherapy.
Cancer 63:1912-1917

Kurtz, J., Jacquemier, J., Torhorst, J. et al 1989 Conservation therapy for breast cancers other than infiltrating ductal carcinoma.
Cancer 63:1630-1635

Kurtz,J., Jacquemier, J., Amalric, R. et al 1990 Breast conserving therapy for macroscopically multiple cancers.
Ann Surg 212: 38-44

Kurtz, J., Jacquemier, G., Amalric,R. et al 1990 Risk factors for breast recurrence in premenopausal and postmenopausal patients with ductal cancers treated by conservation therapy.
Cancer 65:1867-1878

Kurtz, J 1992 Factors influencing the risk of local recurrence in the breast.
Eur J Cancer 28(2/3) 660-666

Lewis-Jones, H.,Whitehouse, G., Leinster, S. 1991 The role of magnetic resonance imaging in the assessment of local recurrent breast carcinoma
Clin Radiol 3:197-204

Lindley, R., Bulman, A., Parsons, P. et al 1989 Histologic features predictive of an increased risk of early local recurrence after treatment of breast cancer by local tumour excision and radical radiotherapy.
Surgery 105:13-20

Locker, A., Ellis, I., Morgan, D. et al 1989 Factors influencing local recurrence after excision and radiotherapy for primary breast cancer.
Br J Surg 76:890-894

Low, S., Dixon, A., Bell, J. et al 1992 Tumour oestrogen receptor content allows selection of elderly patients with breast cancer for conservative tamoxifen treatment.
Br J Surg 79:1314-1316

Madden, J.L., Kandelalaft, S., Bourque, R. 1972 Modified radical mastectomy.
Ann Surg 175:624-34

Maiman, T.H. 1960 Stimulated optical radiation in ruby.
Nature 187:493-4.

Malone, D.,Wyman, D., Moote, D. et al 1992 Sonographic changes during hepatic interstitial laser photocoagulation.
Invest Radiol 27::

Mason, B.H., Holdaday, I.M., Mullins, P.R. et al 1983 Progesterone and oestrogen receptors as prognostic variables in breast cancer.
Cancer Res. 43:2985-90.

Masters, A. *MS thesis(University of London) 1994*

Masters, A., Steger, A., Bown, S.G. 1991 Role of interstitial therapy in the treatment of liver cancer.
Br J Surg 78:518-523

Masters, A., Bown,S.G.(a) 1990 Interstitial laser hyperthermia in tumour therapy.
Annales Chirurgiae et Gynaecologiae 79:244-251

Masters, A., Bown,S.G.(b) 1990 Interstitial laser hyperthermia in the treatment of tumours
Lasers Med Sci 5:129-135

Mate, T.P., Carter, D., Fischer, D. et al 1986 A clinical and histopathologic analysis of the results of conservation surgery and radiation therapy in stage I and II breast carcinoma
Cancer 58:1995-2002

Mathewson, K., Coleridge-Smith, P., O'Sulivan,J .et al 1987 Biological effects of Nd:YAG photocoagulation in rats.
Gastroenterology 93:550-557.

Mathewson, K., Barr, H., Tralau, C., Bown, S.G. 1989 Low power interstitial laser photocoagulation: studies in a transplantable fibrosarcoma
Br J Surg 76:378-381

Matsumoto, R., Selig ,A., Colucci, V et al 1992 Interstitial Nd-YAG laser ablation in normal rabbit liver: Trial to maximise the size of laser induced lesions.
Lasers Surg Med 12:650-658

McCarthy, M., Bore, J. 1991 Treatment of breast cancer in two teaching hospitals: a Comparison with consensus guidelines.
Eur. J. Cancer 7(5): 579-82.

McCormick, B., Kinne, D., Petrek,J. et al 1987 Limited resection for breast cancer: a study of inked specimen margins before radiotherapy.
Int J Radiat Oncol Biol Phys 13:1667-1671.

McGuire,W.L.,1989 Adjuvant therapy for node negative breast cancer.
N Engl J Med 320:525-527

McGuire,W.L.,Tandon,A.K.,Allred,D.C. et al 1990 How to use prognostic factors in axillary node negative breast cancer patients.
JNCI 83:1006-1015.

McNicholas, M., Mercer, P., Miller, J. et al 1993 Colour doppler sonography in the evaluation of palpable breast masses.
AJR 61:765-771

McNicholas, T., Steger, ,A., Bown, S. 1993 Interstitial laser coagulation of the prostate.
Br J Urol 71:439-444

Medical Directory, 1992 published by the Longman Group U.K.Ltd

Mintum, M. ,Welch, M.,Siegel, B.1988 Breast cancer: PET imaging of estrogen receptors.
Radiology 69:45-48

Morris, J., Royle, G.T., Taylor, I. 1989 Changes in the surgical management of early breast cancer in England.
J. Roy. Soc. Med. 82:12-14

Morris, J., Farmer, A., Royle, G. 1992 Recent changes in the surgical management of T1/2 breast cancer in England.
Eur. J. Cancer 28A,10;1709-12.

Morris, S., Corder, A.P., Taylor, I. 1992 Breast cancer follow up:- Why do we do it ?
Eur.J. Surg. Oncol. 18(4):408-9

Muir, B., Lamb, J., Anderson., T. et al 1983 Microcalcification and its relationship to cancer of the breast; experience in a screening clinic.
Clin Radiol 34:193-200

Mustakallio, S. 1954 Treatment of breast cancer by tumour extirpation and roentgen therapy instead of radical operation.
Journal of the Faculty of Radiologists 6:23-26

Nakamura, S., Nishiwaki, Y , Suzuki, S. et al 1990 Light attenuation of human liver and hepatic tumours after surgical resection.
Lasers Surg Med 10:12-15

Nemoto, T., Vana, J., Bedwani, R.et al 1980 Management and survival of female breast cancer: Results of a national survey by the American College of Surgeons.
Cancer 45:2917-2924.

Nolsoe, C., Torp-Pedersen, S., Olldag, E. et al 1992 Bare fibre low power Nd-YAG laser interstitial hyperthermia. Comparison between diffuser tip and non-modified tip. An in vitro study.
Lasers Med Sci 7:1-7

Nugent, P, O'Connell, T. 1985 Breast Cancer and Pregnancy.
Arch Surg 120:1221-1224.

O'Dwyer, P.J. 1991 Axillary dissection in primary breast cancer.
BMJ 302:360-61.

O'Reilly, S.M., Richards, M. 1992 Is DNA ploidy a useful investigation in breast cancer
Eur J Cancer 8(2/3)504-507.

Page, D., Dixon, J.., Anderson, T..et al 1983 Invasive cribriform carcinoma of the breast.
Histopathology 7: 525-536

Paik, S., Hazen, R., Fisher, E. et al 1990 Pathologic findings from the National Surgical Adjuvant Breast and Bowel Project: prognostic significance of erb B2 protein over expression in primary breast cancer.
J Clin Oncol 8:103-112

Pain, J., Ebbs, S., Hern, R. et al 1992 Assessment of breast cancer size: A comparison of methods.
Eur J Sug Oncol 18:44-48

Panjehpour, M., Overholt,B., Milligan,A. et al 1990 Nd-YAG laser induced interstitial hyperthermia using a long frosted contact probe.
Lasers Surg Med 10:16-24

Patey, D.H., Dyson, W.H. 1948 The prognosis of carcinoma of the breast in relation to the type of operation performed
Br. J. Cancer 2:7-13.

Pearson, O.H., Gordon, N., Hubay, C.et al,1985 Oestrogen receptors and prognosis of breast cancer. In *Holland,V.P.editor.Hormonally responsive tumours.*
Orlando:Academic press 487-503

Pedersen, L., Holck, S., Schiodt, T. 1988 Medullary carcinoma of the breast.
Cancer Treat. Rev. 15:53-63.

Peters, G.,Wolff, M., Haagenson, C. 1981 Tubular carcinoma of the breast - Clinical pathologic correlations based on 100 cases
Ann Surg 193:138-149.

Petrek,J ., Dukoff, R., Rogatko, A.1991 Prognosis of pregnancy associated breast cancer.
Cancer 67:869-872.

Pettingale, J., Morris, T., Greer, S. et al 1985 Mental attitudes to cancer: an additional prognostic factor.
Lancet i:170.

Pierce W., Harms, S., Flamig, D. et al 1991 Three dimentional Gadolinium enhanced MR imaging of the breast:Pulse sequence with fat suppresion and magnetisation transfer contrast.
Radiology 181:757-763

Porritt, A. 1964 Early carcinoma of the breast.
Br. J Surg 51:214-216.

Powles,T., Jones, A., Ashley, S et al 1989 Menstrual effect on surgical cure of breast cancer
Lancet ii:1343-44.

Preece, P., Wood, R., Mackie, C., Cushieri, A. 1982 Tamoxifen as the sole treatment for localised breast cancer in elderly women.
BMJ 284:869-70.

Ramirez, A., Craig,T.,Watson, J. et al 1989 Stress and relapse of breast cancer.
BMJ 298:291-293.

Recht, A., Connolly, J.L., Schnitt, S. et al 1988 The effect of young age on tumour recurrence in the treated breast after conservation surgery and radiotherapy.
Int J Radiat Oncol Biol Phys, 14:3-10

Redard, M., Vassilakos, P., Weintraub, J. et al 1989 A simple method for oestrogen receptor antigen preservation in cytologic specimens containing breast carcinoma cells.
Cytopathology 5:188-193

Remvikos,Y., Vielh, P., Padoy, E. et al 1991 Breast cancer proliferation measured on cytological samples: a study by flow cytometry of S-phase fractions and BrdU incorporation.
Br J Cancer 64:501-507

Report from the Yorkshire Breast Cancer Group. Critical assessment of the clinical TNM system in breast cancer.1980
BMJ 2:134-136

Ridolfi, R.L., Rosen, P.P., Port, A. et al 1977 Medullary carcinoma of the breast - a clinicopathological study with a ten year follow up.
Cancer 40 1365-1385.

Robertson, J., Todd, J., Ellis, I. et al 1988 Comparison of mastectomy with tamoxifen in treating elderly patients with operable breast cancer.
BMJ 297:511-514

Rosen, P.,Wang,T. 1980 Colloid carcinoma of the breast. Analysis of 64 patients with long follow up.
Am J Clin Pathol 73:30

Rosen, P., Groshen, S., Saigo, P. et al 1989 Pathologic prognostic factors in stage I(T1N0M0) and stage II(T1N1M0) breast carcinoma: A study of 644 patients with a median follow up of 18 years.
J Clin Oncol 7:1239-1251.

Rutgers, E.J., van-Slooten, E.A., Kluck, H.M. 1989 Follow up after treatment of primary breast cancer.
Br. J. Surg. 76: 187-90.

Ryoo, M., Kagan, R., Wollin, M. et al 1989 Prognostic factors for recurrence and cosmesis in 393 patients after radiation therapy for early mammary carcinoma.
Radiology 172:555-559

Sacks, N., Baum, M. 1993 Primary management of carcinoma of the breast.
Lancet 42:1402-1408

Sacks, N., Barr, L.C., Allan, S.M., Baum, M. 1992 The role of axillary dissection in operable breast cancer.
Breast, 1: 41-9.

Sainsbury, J., Round, C.1992 Timing of surgery for breast cancer and menstrual cycle.
Breast 1(3),152.

Sainsbury,J ., Needham, G.K., Farndon, J.R. et al 1987 Epidermal growth factor receptor status as a predictor of early recurrence and death from breast cancer.
Lancet, 1:1398-1402.

Sarrazin, D., Le, M., Rouesse, J. et al 1984 Conservative treatment versus mastectomy in breast cancer tumors with macroscopic diameter of 20 millimetres or less.
Cancer 53: 1209-13

Sarrazin, D., Le, M., Arriagada, R. et al 1989 Ten year results of a randomised trial comparing a conservative treatment to mastectomy in early breast cancer.
Radiother Oncol 14:177-184

Saunders, C.M., Baum, M.,1993 Breast cancer and pregnancy: a review
J Roy Soc Med 86:162-165

Schatz, S., Bown, S.G.,Wyman, D. et al 1992 Low power interstitial Nd-YAG laser photocoagulation in normal rabbit brain.
Lasers Med Sci 7:433-439

Schmidt-Ullrich, R., Wazer, D., Tercilla, O. et al 1989 Tumor margin assessment as a guide to optimal conservation surgery and irradiation in early stage breast carcinoma.
Int J Radiat Oncol Biol Phys 17:733-738

Schnitt, S., Connolly, J., Khettry, U. et al 1987 Pathologic findings on re-excision of the primary site in breast cancer patients considered for treatment by primary radiation therapy.
Cancer 59:675-681

Schnitt, S.J., Connolly, J., Recht, A. et al 1989 Influence of infiltrating lobular histology on local tumour control in breast cancer patients treated with conservative surgery and radiotherapy
Cancer 64:448-454

Schottenfield, D., Nash, A., Robbins, G. et al 1976 Ten year results of the treatment of primary operable breast cancer.
Cancer 38:1001-1007.

Senie, R., Rosen, P., Rhodes, P.et al 1991 Timing of breast cancer excision during the menstrual cycle influences duration of disease free survival.
Ann Intern Med 15:337-42.

Sickles, E., Filly, R., Callen, P. 1983 Breast cancer detection with sonography and mammography: Comparison using state of the art equipment.
AJR 140:843-845

Sigurdsson, H., Baldetorp, B., Borg, A.et al 1990 Indicators of prognosis in node negative breast cancer.
N Engl J Med 322:1045-1053.

Slamon, D., Clark, G.M., Wong, S.G. et al 1987 Human breast cancer: Correlation of relapse and survival with amplification of her-2/neu oncogene.
Science, 235:177-182.

Solin, L., Fowble, B., Schultz, D. et al 1991 The significance of the pathology margins of the tumour excision on the outcome of patients treated with definitive irradiation for early stage breast cancer.
Int J Rad Oncol Biol Phys 21:279-287

Spyratos, F., Brouillet, J.P., DeFreeno, J. et al 1989 Cathepsin D: an independent prognostic factor for metastases of breast cancer.
Lancet 2:1115-1118.

Steele, R., Forrest,A., Gibson,T., et al 1985 The efficacy of lower axillary sampling in obtaining lymph node status in breast cancer; a controlled randomised trial.
Br. J. Surg. 72:368-369

Steger, A.C., Lees, W.R., Walmsley, K. et al 1989 Interstitial laser hyperthermia: a new approach to local destruction of tumours
BMJ 299:362-365

Steger, A.C., Lees,W.R., Shorvon, P.et al 1992 Multiple fibre low power interstitial laser hyperthermia: studies in the normal liver.
Br J Surg 79:139-145

Steger, A., Shovron, P.,Walmsley, K., Chisholm, R.et al 1992 Ultrasound features of low power interstitial laser hyperthermia.
Clin Radiol 46:88-93

Stomper, P., Connolly, J. 1991 Mammographic features predicting an extensive intraductal component in early stage infiltrating ductal carcinoma.
AJR 158:269-272

Svaasand, L., Boerslid, T., Oeveraasen, M. 1985 Thermal and optical properties of living tissue: Application to laser induced hyperthermia.
Lasers Surg Med 5:589-602

Tandon, A., Clark, G., Chamness, G. et al 1990 Cathepsin D and prognosis in breast cancer.
N Engl J Med 322:297-302

Thomsen, S. 1991 Pathologic analysis of photothermal and photomechanical effects of laser tissue interactions.
Photochem Photobiol 53:825-835

Thorpe, S., Rochefort, H., Garcia, M. et al 1989 Association between high concentration of Mr 52,000 cathepsin D and poor prognosis in primary human breast cancer.
Cancer Res. 49:6008-6014

Thurell, W., Amin, Z., Maddox, P. et al Histopathological features of laser induced necrosis in rat liver: a zone of in-situ fixation.
Histochemistry(in press)

Todd, J.H., Dowle, C., Williams, M. et al,1987 Confirmation of a prognostic index in primary breast cancer
Br J Cancer 56:489-492

du Toit, R.S., Locker, A.P., Ellis, I.O. et al 1991 An evaluation of the differences in prognosis, recurrence patterns and receptor status between invasive lobular and other invasive carcinomas of the breast.
Eur J Surg Oncol 17:251-257

Tracz, R., Wyman, D., Little, P. et al 1993 Comparison of magnetic resonance images and the histological findings of lesions induced by interstitial laser photocoagulation in the brain.
Lasers Surg Med 13;45-54

Treteli, S., Haldorsen, T., Ottestad, L.1990 The effect of pre-morbid height and weight on the survival of breast cancer patients.
Br J Cancer 62:299-303.

Urban, J.A., Baker, H.W. 1952 Radical mastectomy in continuity with an en bloc resection of the internal mammary lymph node chain.
Cancer 5 :992.

Valagussa, P., Bonadonna, G., Veronesi, U.1978 patterns of relapse and survival following radical mastectomy.
Cancer 41:1170-1178.

Van Eeden, P., Steger, A.C., Bown, S.G. 1988 Fibre tip considerations for low power laser interstitial hyperthermia
Lasers Med Sci 3:336(Abstract)

Van Limbergen, E. Van der Bogaert, W., Van der Schueren, E. et al 1987 Tumour excision and radiotherapy as primary treatment of breast cancer. Analysis of patient and treatment parameters and local control.
Radioth Oncol 8:1-9

Van Limbergen,E., Van der Schueren,E., Van der Bogaert, W. et al 1990 Local control of operable breast cancer after radiotherapy alone.
E ur J Cancer 26(6):674-679

Veronesi, U., Saccozzi, R., Del Vecchio, M. et al 1981 Comparing radical mastectomy with quadrantectomy, axillary dissection and radiotherapy in patients with small cancers of the breast.
N Engl J Med 305:6-11

Veronesi, U., Cascinelli, N., Greco, M., 1985 Prognosis of breast cancer after mastectomy and dissection of internal mammary nodes.
Ann Surg 202:702-707.

Veronesi, U., Luini, A., Galimberti,V. et al 1990 Extent of metastatic axillary involvement in 1446 cases of breast cancer.
Eur.J.Surg.Oncol. 16;127-133.

Veronesi, U., Banfi, A., Salvadori, B. et al 1990 Breast conservation is the treatment of choice for small breast cancers: long term results of a randomised trial.
Eur J Cancer 26(6) 668-670

Veronesi, U., Volterrani, F., Luini, A. et al 1990 Quadrantectomy versus lumpectomy for small size breast cancer.
Eur J Cancer 26(6):671-673

Vicini, F.A., Eberlein, T.J., Connolly, J.L. et al 1991 The optimal extent of resection for patients with stage I or II cancer treated with conservative surgery and radiotherapy.
Ann Surg 214:200-205

Walker, R.A., Gullick,W.J., Garley, J. 1989 An evaluation of immune reactivity for c-erbB2 protein as a marker of poor short term prognosis in breast cancer.
Br J Cancer 60:426-429

Wangensteen, O.H. 1949 Remarks on extension of the Halsted operation for cancer of the breast.
Ann Surg 130:315.

Warren, S. 1930 A roentgenologic study of the breast
Am J Roentgenol Rad Ther 24:113-124

Weigand, R.A., Isenberg, W.M., Russo, J. et al 1982 Blood vessel invasion and axillary lymph node involvement as prognostic indicators for human breast cancer.
Cancer 50:962-996??

Weintraub, J., Weintraub, D., Redard, M. et al 1987 Evaluation of oestrogen receptors by immunocytochemistry on fine needle aspiration biopsy specimens from breast tumours.
Cancer 60:1163-1172

Wilkinson, E., Hause, L., Kuzma, J. et al 1983 Occult axillary lymph node metastases in patients with invasive breast cancer.
Lab Invest. 44; 83A

Wilson, R.E., Donegan, W.L., Mettlin, C. et al 1984 The 1982 survey of carcinoma of the breast in the United States by the American College of Surgeons
Surg Gynecol Obstet 159:309-312

Wilson, R., Hart, A., Dawes, P., 1988 Mastectomy or conservation: the patient's choice.
BMJ 97:1167-1169

Wyman, D., Whelan, W., Wilson, B.C. 1992 Interstitial laser photocoagulation :Nd:YAG 1064 nm optical fibre source compared to point heat source.
Lasers Surg Med 12(6)659-664

Young, J.,1989 Incidence and mortality of breast cancer. In *Breast Cancer*. Ed B.Kennedy.Alan Liss, New York pp1-5.

Zafrani, B., Vielh, P., Fourquet, A. et al 1989 Conservative treatment of early breast cancer: Prognostic value of the ductal in situ component and other pathological variables on local control and survival.
Eur J Cancer Clin Oncol 25(11):1645-1650

Zwaveling, A., Albers, G., Felthius, W., Hermans, J. 1987 An evaluation of routine follow up for detection of breast cancer recurrence.
J. Surg. Oncol. 34;194-7

Publications and presentations whilst at the National Medical Laser Centre, January 1992-March 1994

Chapters in books

1) "Prognostic factors in Early Breast Cancer"
S.A.Harries in *Recent Advances in Surgery, 1994, volume 17. Chapter 7 pp 105-120. Published by Churchill Livingstone.* Editors I.Taylor and C.D.Johnson(in press)

Original Publications;

1) "Interstitial laser photocoagulation as a treatment for breast cancer."
Harries,S.A., Amin,Z., Lees,W.R., Cooke, J., Cook, M.G., Smith, M.E.F., Scurr, J.H., Kissin, M.W. and Bown, S.G..
British Journal of Surgery(in press)

2) "Low power interstitial laser photocoagulation for breast cancer."
Harries,S.A., Amin,Z., Lees,W.R., Cooke,J., Smith,M.E.F., Cook,M.G., Scurr,J.H., Kissin,M.W. and Bown, S.G..
SPIE proceedings, Laser interactions with hard and soft tissues, 1994 ;2077:101-108

3) "Interstitial tumour photocoagulation."
Amin,Z., **Harries,S.A.**, Bown,S.G.
Endoscopic Surgery And Allied Technologies ,1993;1:224-229.

4) "Interstitial laser photocoagulation in rat liver: Importance of fibre type, laser wavelength and tissue charring."
Amin, Z., Buonaccorsi,G., Mills,T., **Harries,S.**, Lees,W., Bown,S.G
SPIE Proceedings, Laser Tissue Interaction IV, 1993, 1882;172-182

5) "Interstitial laser photocoagulation : Evaluation of a 1320 nm Nd;YAG and an 805 nm diode laser, the significance of charring, and the value of pre-charring the fibre tip."
Amin,Z., Buonaccorsi,G., Mills,T., **Harries,S.A.**, Lees,W.R.
Bown,S.G.
Lasers In Medical Science ,1993 ;8:113-120

6) "CT- Pathologic assessment of laser induced necrosis in rat liver."
Amin,Z., Thurell,W., Spencer,G., **Harries,S.A.**, Grant,W.,
Bown,S., Lees,W.R.
Investigative Radiology(in Press)

7) "Breast MRI: a review of the current status and potential future applications."
Harms,S., Flemig, P., Bown,S.G., **Harries,S.A.**
American Journal Of Roentgentology (In Press)

Papers submitted or in preparation

1) "Histopathological features of laser induced necrosis in rat liver: The concept of in-situ fixation."*(Submitted to Histochemistry)*
Thurell, W., Amin, Z., Maddox, P., **Harries,S.A.**, Bown,S.G.

2) "A survey of the management of breast cancer in England and Wales."
Harries,S.A., Lawrence,R.N., Scrivener,R., Fieldman,N.R.
Scurr,J.H., Kissin,M.W. *(Submitted to British Journal of Surgery)*

3) "The workload of British breast cancer surgeons."
S.A.Harries, R.N.Lawrence, R.Scrivener, N.R.Fieldman,
M.W.Kissin and T.Bates.*(Submitted to British Medical Journal)*

5) "Histological features of laser induced necrosis in breast cancer."
Harries,S.A., Thurell, W., Amin,Z.,Cook,M.G., Smith,M.E.F.,
Kissin,M.W. and S.G.Bown.*(in preparation)*

6) "Radiological features of ILP: a comparison of ultrasound, CT and MRI with pathological correlation."
Harries,S.A., Amin,Z., Lees,W.R., Cooke,J., Cook,M.G., Smith,M.E.F.,
Scurr,J.H., Kissin,M.W. and S.G.Bown.*(in preparation)*

Letters:

1) "Regional variations in the surgical treatment of early breast cancer."
Harries,S.A., Scrivener,R., Lawrence,R.N, Kissin,M.W
British Journal Of Surgery, 1993;80(6):809

Published abstracts:

1) "Interstitial laser hyperthermia for breast cancer."
Harries,S.A., Masters,A., Lees,W., Cooke,J., Cook,M., Smith,M., Scurr,J., Kissin,M., Bown,S.
Minimally Invasive Therapy Journal(Supp),1992;1:81.

2) "Interstitial laser hyperthermia for breast cancer."
Harries,S.A., Masters,A., Lees.W., Cooke.J., Cook,M. Smith,M. Scurr,J., Kissin,M., Bown,S.G.
European Journal Of Surgical Oncology,1993, 19(2):216-217

3) "The investigation and treatment of breast cancer in England and Wales."
Harries,S.A., Lawrence,R.N., Scrivener,R., Fieldman,N.R. Scurr,J.H., Kissin,M.W.
European Journal Of Surgical Oncology, 1993, 19(5);504

4) "The Investigation and treatment of breast cancer in England and Wales."
Harries,S.A., Lawrence,R.N., Scrivener,R., Fieldman,N.R. and Kissin,M.W.
British Journal Of Surgery, 1993, 80(Suppl.);S12

5) " Interstitial laser photocoagulation for breast cancer."
Harries,S.A., Amin,Z., Lees,W., Cooke,J., Cook,M., Smith,M., Scurr,J.H., Kissin,M.W., Bown,S.G.
British Journal Of Surgery(In Press)

Presentations:

1) "Interstitial laser hyperthermia in the treatment of breast cancer."
Harries,S.A., Masters,A., Lees,W., Scurr,J., Cooke,J., Smith,M. Cook,M., Kissin,M., Bown,S.G.
Society Of Minimally Invasive Therapy International Meeting, Dublin, November 1992.

2) "Interstitial laser hyperthermia for breast cancer"
Harries,S.A., Masters,A. Lees,W., Cooke,J., Cook,M., Smith,M.,

Scurr,J., Kissin,M., Bown,S.G.

British Association Of Surgical Oncology,

Charing Cross Hospital, London, November 1992.

3) "Interstitial laser photocoagulation in rat liver: Importance of fibre type, laser wavelength,and tissue charring."

Z.Amin, G.Buonaccorsi, T.Mills, **S.A.Harries,** W.R.Lees and S.G.Bown.

SPIE Meeting, Los Angeles, U.S.A., January 1993.

4) "Identifying trainers of breast surgeons in England and Wales."

S.A.Harries, M.W.Kissin,R.Lawrence,N.R.Fieldman,

R.Scrivener and Tom Bates.

British Association Of Surgical Oncology (BASO) Breast Screening Group (Big18), Charing Cross Hospital , London, January 1993.

5) "Interstitial Laser Photocoagulation for Breast Cancer."

S.A.Harries, A.Masters, Z.Amin, W.Lees, J.Cooke, M.Cook,

M.Smith, J.H.Scurr, M.W.Kissin and S.G.Bown.

Institute Of Physics Annual Congress, Brighton, April 1993

6) "The investigation and treatment of breast cancer in England and Wales."

S.A.Harries, R.N.Lawrence, R.Scrivener, N.R.Fieldman,

J.H.Scurr and M.W.Kissin

British Association Of Surgical Oncology , 46th Meeting

Glan Clwyd Hospital, Rhyl, North Wales, June 1993.

7) "The investigation and treatment of breast cancer in England and Wales."

S.A.Harries, R.N.Lawrence, R.Scrivener, N.Fieldman,

and M.W.Kissin

Eurosurgery, The South Bank, London, September 1993

8) "Interstitial laser photocoagulation for breast cancer."

Harries,S.A., Amin,Z., Lees,W., Cooke,J., Cook,M., Smith,M., Scurr,J.H., Kissin,M.W., Bown,S.G.

Eurosurgery, The South Bank, London, September 1993.

9) "Interstitial laser photocoagulation for breast cancer."

Harries,S.A., Amin,Z., Lees,W., Cooke,J., Cook,M., Smith,M., Scurr,J.H., Kissin,M.W., Bown,S.G.

Europto(SPIE) European Conference, Budapest, Hungary, September 1993.

10) "A survey of the treatment of breast cancer in England and Wales in 1992."

S.A.Harries, R.N.Lawrence, R.Scrivener, N.R.Fieldman, J.H.Scurr, and M.W.Kissin.

Nottingham/EORTC Joint Breast Cancer Meeting, Nottingham, September 1993.

Posters:

1) "Interstitial laser hyperthermia for breast cancer."

S.A.Harries, A.Masters, W.R.Lees, J.H.Scurr, S.G.Bown, M.W.Kissin

Imperial Cancer Research Fund Review, London, Febuary 1992.

2) "Interstitial laser hyperthermia for breast cancer."

S.A.Harries, A.Masters, W.Lees., J.H.Scurr, J.Cooke, M.Cook, M.W.Kissin, S.G.Bown

Alumnus Day,University College London,June 1992

3) " Interstitial laser photocoagulation for the treatment of tumours."

S.A.Harries, Z.Amin, W.Lees, J.Cooke, M.Cook,

M.Smith, M.W.Kissin and S.G.Bown.

Science into industry exhibition, The Royal Society, London, May 1993.

4) "Local recurrence following conservative surgery and radiotherapy for early breast cancer-experience of University College and Middlesex Hospitals "

S.A.Harries, H.Lyons-Swanson, T.Davidson, G.Sadler, J.S.Tobias, M.Spittle and I.Taylor.

CRC Communication and Counselling Research Centre opening exhibition, London, March 1994

5) " MR imaging of Interstitial laser photocoagulation of breast cancer"

M.Clemence, **S.A.Harries**, Z.Amin, S.G. Bown

International MRI conference, Nottingham, April 1994.

Invited lectures:

1) "Interstitial laser hyperthermia for breast cancer."

S.A.Harries, S.G.Bown.

Guys Hospital Clinical Oncology unit May 1992.

2) "Interstitial laser hyperthermia, clinical application in breast disease."

S.A.Harries

Gordon Research Conference, Lasers in Biology, New Hampshire, United States of America, July 1992.

3) "Laser treatment of breast cancer."

S.A.Harries

Academic department of surgery, The Whittington Hospital, London, September 1992.

4) "Interstitial laser hyperthermia for breast cancer."

S.A.Harries,

ICRF breast cancer sudy day, Guy's Hospital, London, October 1992.

5) "Laser treatment of breast cancer."

S.A.Harries, ZAmin

Northwick Park Hospital, Harrow, January 1993

6) "The use of lasers in general surgery."

S.A.Harries

Whittington Hospital, London , February 1993

7) "The workload of British breast cancer surgeons."

S.A.Harries, R.N.Lawrence, R.Scrivener, N.R.Fieldman,

M.W.Kissin and T.Bates.

In service training day for breast cancer surgeon(BASO),

Glan Clwyd Hospital, Bodelwyddan, Rhyl, North Wales, June 1993.

8) "The treatment of breast cancer in England and Wales."

S.A.Harries, R.N.Lawrence, R.Scrivener, N.R.Fieldman, J.H.Scurr

and M.W.Kissin.

Regional meeting on consenus management of early breast cancer,

University College Hospital, July 1993.

9) "The 805nm Diode laser: Experimental work and clinical applications."

S.A.Harries, Z.Amin.

SPIE workshop on the surgical applications of the diode laser, Budapest,

Hungary. September 1993.

10) "Interstitial laser photocoagulation for breast cancer."

S.A.Harries

Breast cancer Imaging symposium, University of Toronto, Canada, October 1993.

11) "Interstitial laser photocoagulation: Experimental data and clinical applications in the treatment of liver, breast, pancreatic and prostate cancer."

S.A.Harries, ZAmin and S.G.Bown.

Mount Sinai Hospital, Toronto, Canada. Division of Medicine and Surgery, October 1993.

12) "Interstitial laser photocoagulation for breast cancer"

S.A.Harries, Z Amin and S.G.Bown

The Royal Marsden Hospital, London, November 1993.

Television and radio presentations:

1. "Toasted tumours" about laser treatment of breast cancer for "*Beyond 2000*", *Australian Broadcasting Corporation* June 1992.
2. "Laser treatment of breast cancer" . *BBC radio Surrey News*, January 5th 1993.
3. " Image guided lasers will kill breast tumours without surgery". *San Francisco Chronicle*, March 30th 1993.
4. "The Diomed Diode Laser",*The Daily Telegraph*, April 29th 1993
5. "Interstitial laser photocoagulation in the treatment of tumours", *Science Now, BBC Radio 4* , May 15th 1993
6. " Interstitial laser treatment of tumours", *Oncology Times, New York* 1993
7. "Breast op laser fuels optimism on cancer", *Hospital Doctor*, September 1993
8. "Laser treatment of breast cancer", *Canadian Medical Post*, October 1993
9. "Laser treatment of breast cancer", *Ontario Medicine, Canada* . October 1993
10. "Laser treatment of tumours", *Malta Times*, March 1994
11. "The breast cancer lottery", *BBC1 Panorama*, March 20th 1994

A LITTLE LIGHT RELIEF !

(from an American Science fiction magazine; courtesy of Mr.Mark Kissin)