INTERSTITIAL LASER PHOTOCOAGULATION OF
LIVER METASTASES

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ABSTRACT

The treatment of liver metastases is presently unsatisfactory; many patients receive no specific therapy because of the significant morbidity associated with current treatments which have no proven survival advantage. Interstitial laser photocoagulation (ILP) is a percutaneous technique of in situ liver tumour destruction by heat, using low power laser energy which is delivered via thin flexible optical fibres.

In this thesis the potential of ILP to effectively treat liver metastases was investigated, and the aims of the thesis were: (a) to clarify the mechanism of action of ILP; (b) to improve the laser parameters and safely increase the extent of thermal damage; (c) to accurately assess the extent of thermal damage radiologically and histologically; (d) to evaluate the clinical application of ILP.

One hundred and fifty six Wistar rats and two Large White pigs had ILP to their livers. The parameters evaluated were fibre size and material, different laser wavelengths, and fibre-tip alterations. Significant findings were that tissue charring around the fibre-tip was associated with greater thermal damage, and that new less penetrating wavelengths produced larger necrotic lesions than the 1064nm wavelength, contrary to previously held beliefs. Histological assessment demonstrated the unexpected finding of a zone of heat-fixed hepatocytes, outside which were necrotic cells. A computed tomography (CT)-pathologic study showed that the extent of the tissue density changes seen on CT corresponded to the extent of thermal damage pathologically.

Ninety three liver metastases in 31 patients were treated with ILP. Monitoring by ultrasound showed the thermal change as an irregular echogenic zone during ILP, and dynamic CT demonstrated the laser-induced necrosis as a new area of non-enhancement 24hrs or more afterwards. Necrosis of tumour volume was more than 50% in 89% (83 of 93) of the tumours, and 100% necrosis was achieved in 55% (51 of 93). Tumours smaller than 4cm were treated more effectively than larger tumours. Complications were minor.

ILP continues to evolve as a minimally invasive technique of in situ tumour destruction. This thesis highlights important new concepts on the mechanism of action of ILP, and the clinical evaluation has shown that ILP can, at present, safely and effectively destroy small liver metastases (2cm or less in diameter). The current drawbacks of the technique are discussed and potential solutions suggested.
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DEDICATION

To my parents
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The work for this thesis was carried out at the National Medical Laser Centre, University College London, and the Department of Radiology, The Middlesex Hospital. My supervisors were Professor SG Bown and Dr WR Lees; I am greatly indebted to them both for the support and encouragement they gave me throughout the project. Dr Lees provided the opportunity for me to begin this research, and was always willing to discuss the experimental and clinical work. Professor Bown allowed me to work at the Laser Centre and gave invaluable guidance throughout my time there; I particularly appreciated his ability to read and quickly return draft papers and thesis text usually within a few days, with very useful critical comments.

Several people have contributed significant time and effort in allowing me to start and complete this research. I am especially grateful to Dr Giovanni Buonaccorsi for his enthusiasm towards the experimental work and for the many hours he spent discussing and helping with the experiments, as well as preparing the lasers for the clinical work. Dr Tim Mills also exchanged several useful ideas for the experimental work. Dr Wendy Thurrell and Mr Peter Maddox helped with preparing and interpreting the histological material. Mr Mike Tighe assisted with the experimental and clinical CT scans, and Dr Jenny Donald helped with assessing the clinical CT scans in the earlier period of this research. Mr C Keast and his staff in Biological Services, particularly Mr Andrew Grieve and Miss Sharon Anthony, were of great help with the animal work. All of the illustrations in this thesis were produced with assistance from the Medical Photography departments at University College London and The Middlesex Hospital.

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Financial support during this research was given by the Papadakis Trust.
STATEMENT OF ORIGINALITY

All of the experimental work (section B) in this thesis was my own. The series of experiments (chapter 4) which led to the new concept of the mechanism of action of ILP was based on my own preliminary observations. The experimental protocols were planned following discussions with Professor SG Bown, Dr G Buonaccorsi and Dr T Mills, and the experiments carried out by me with laser support given by Dr Buonaccorsi. Mr SA Harries performed the laparotomy on the pigs; I assisted and performed ILP to the pig liver lobes. The CT-pathologic correlative study (chapter 5.2) was my own idea and planned with the help of Dr WR Lees and Professor Bown; the study was carried out by me and Mr M Tighe assisted with the CT scans. The histopathological evaluation of ILP (chapter 5.1) was my own idea and planned with Professor Bown and Dr W Thurrell; the histological assessment was made by Dr Thurrell.

The clinical work was part of an ongoing program. Two of my predecessors (Mr AC Steger and Mr A Masters) were involved with treating the first 10 patients. I have continued to treat 5 of these patients, and included the results of the other 5 patients in a detailed analysis of all of the clinical data. In addition, I have treated and followed up a further 21 patients. Therefore, I have been involved with treating and evaluating 26 of the 31 patients reported in this thesis, and the data from all 31 patients was analysed by me.

The results of the experimental and clinical sections of this thesis have contributed significantly to the development of ILP. The experimental findings have changed the concept of the mechanism of action of ILP, and the clinical work represents the largest series of patients with liver metastases treated by ILP.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ALP</td>
<td>alkaline phosphatase</td>
</tr>
<tr>
<td>AXIS</td>
<td>adjuvant X-ray and 5-FU infusion study</td>
</tr>
<tr>
<td>CA19.9</td>
<td>carbohydrate antigen 19.9</td>
</tr>
<tr>
<td>CEA</td>
<td>carcinoembryonic antigen</td>
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<tr>
<td>CNS</td>
<td>central nervous system</td>
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<tr>
<td>CT</td>
<td>computed tomography</td>
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<tr>
<td>CTAP</td>
<td>CT arterial portography</td>
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<tr>
<td>CTHA</td>
<td>CT hepatic arteriography</td>
</tr>
<tr>
<td>DTPA</td>
<td>diethylene triamine penta-acetic acid</td>
</tr>
<tr>
<td>EOE</td>
<td>ethiodised oil emulsion</td>
</tr>
<tr>
<td>FDG</td>
<td>fluorine-18-labelled deoxyglucose</td>
</tr>
<tr>
<td>FLASH</td>
<td>fast low angle shot</td>
</tr>
<tr>
<td>FOV</td>
<td>field of view</td>
</tr>
<tr>
<td>5-FU</td>
<td>5-fluorouracil</td>
</tr>
<tr>
<td>FUDR</td>
<td>floxuridine</td>
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<tr>
<td>G</td>
<td>gauge</td>
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<tr>
<td>GaAlAs</td>
<td>gallium aluminium arsenide</td>
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<tr>
<td>H &amp; E</td>
<td>haematoxylin and eosin</td>
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<tr>
<td>HAPS</td>
<td>hepatic arterial perfusion scintigraphy</td>
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<tr>
<td>Hb</td>
<td>haemoglobin</td>
</tr>
<tr>
<td>5-HIAA</td>
<td>5-hydroxyindoleacetic acid</td>
</tr>
<tr>
<td>HIFU</td>
<td>high intensity focused ultrasound</td>
</tr>
<tr>
<td>HU</td>
<td>Hounsfield unit</td>
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<tr>
<td>ILH</td>
<td>interstitial laser hyperthermia</td>
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<tr>
<td>ILP</td>
<td>interstitial laser photocoagulation</td>
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<tr>
<td>IOUS</td>
<td>intra-operative ultrasound</td>
</tr>
<tr>
<td>IVC</td>
<td>inferior vena cava</td>
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<tr>
<td>MnDPDP</td>
<td>manganese dipyridoxal diphosphate</td>
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<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>Nd:YAG</td>
<td>neodymium yttrium aluminium garnet</td>
</tr>
<tr>
<td>NADPH</td>
<td>nicotinamide adenine dinucleotide phosphate</td>
</tr>
<tr>
<td>PET</td>
<td>positron emission tomography</td>
</tr>
<tr>
<td>PALA</td>
<td>phosphonacetyl-L-aspartate</td>
</tr>
<tr>
<td>PHR</td>
<td>percentage hepatic replacement</td>
</tr>
<tr>
<td>RASE</td>
<td>rapid acquisition spin echo</td>
</tr>
<tr>
<td>RF</td>
<td>radiofrequency</td>
</tr>
<tr>
<td>ROI</td>
<td>region of interest</td>
</tr>
<tr>
<td>SMA</td>
<td>superior mesenteric artery</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<td>--------------</td>
<td>--------------------------------------------------</td>
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<tr>
<td>SPECT</td>
<td>single photon emission computed tomography</td>
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<tr>
<td>TE</td>
<td>echo time</td>
</tr>
<tr>
<td>TR</td>
<td>repetition time</td>
</tr>
<tr>
<td>T1W</td>
<td>T1 weighted</td>
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<tr>
<td>T2W</td>
<td>T2 weighted</td>
</tr>
<tr>
<td>UKCCCR</td>
<td>UK co-ordinating committee on cancer research</td>
</tr>
<tr>
<td>UICC</td>
<td>international union against cancer</td>
</tr>
<tr>
<td>US</td>
<td>ultrasound</td>
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OVERALL OBJECTIVE OF THESIS

To safely and effectively destroy human liver metastases by ILP, to define which tumours are most suitable for this treatment (in terms of number, size and position), how they should be treated (optimal laser parameters and fibre-tips), and how best to evaluate the results of therapy.
SECTION A: BACKGROUND

CHAPTER 1: LIVER METASTASES: DETECTION, NATURAL HISTORY AND TREATMENT.

CHAPTER 2: INTERSTITIAL LASER PHOTOCOAAGULATION (ILP): REVIEW.

CHAPTER 3: CURRENT DEFICIENCIES IN KNOWLEDGE OF ILP, AND AIMS OF THESIS.
CHAPTER 1: LIVER METASTASES: DETECTION, NATURAL HISTORY AND TREATMENT

Introduction

1.1. Detection of liver metastases
   1.1.1. Biochemical tests
   1.1.2. Imaging
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1.2. Natural history of liver metastases
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   1.3.2. Systemic chemotherapy
   1.3.3. Regional treatments
   1.3.4. Local treatments
   1.3.5. Conclusions
INTRODUCTION

Liver metastases occur in over 40% of all malignancies (Pickren et al, 1982), with affected patients having a poor overall prognosis.

The commonest primary tumour to metastasise to the liver is colorectal cancer. In the UK, there are 28000 new cases of colorectal cancer each year (Cancer Research Campaign, 1991), and over 17000 people die annually with this condition, making it the second most common cause of cancer death (OPCS, 1990). The main cause of treatment failure for patients with colorectal cancer is liver metastases, and these will develop in over 50% of patients (Kelly and Daly, 1992); 20% of patients will have metastases confined to the liver (Weiss et al, 1986).

The majority of patients with liver metastases have advanced disease, with a survival of under 10 months. However, some patients have slow growing liver metastases, which are usually from colorectal primaries, but have also been reported from patients with renal or endocrine primaries (Blumgart and Studley, 1988). These patients are potentially curable by surgical resection of their secondary tumour, provided they have limited disease and no extra-hepatic tumour is present. About 5-10% of patients with colorectal cancer will eventually have resectable liver metastases (Scheele, 1993), with a reported 5 year survival after surgery of 20-30% (Cady and Stone, 1991). Patients with limited liver metastases from colorectal cancer who do not undergo resection rarely survive for more than 2 years after diagnosis (Adson et al, 1984).

Many patients with slow growing liver metastases and limited tumour volume do not have surgery (Allen-Mersh, 1989), either because of a nihilistic attitude of many clinicians towards metastatic disease (Larner, 1991), or the tumour may be adjacent to vital structures, or the patient may be unfit for surgery. Furthermore, recurrence occurs in up to 70% of patients who do have surgery (Greenway, 1988).

It is for these reasons that there is increasing interest in a variety of new treatment modalities for the large number of patients who may potentially benefit - these include new systemic chemotherapy regimes, as well as regional and local liver tumour therapies.

Crucial to treatment planning (especially surgery and local treatments) is accurate and reliable tumour detection, in particular to avoid needless laparotomy. Imaging plays a key role in this and is vital for precise tumour localisation. Indeed, with the rapid advances in imaging technology, far more patients are being detected with earlier, small volume liver tumour.
This introduction has set out the scale of the problem. The remainder of this chapter will discuss the detection of liver metastases, the natural history of untreated tumours, and the various treatment modalities currently available for affected patients. Patients with liver secondaries from colorectal cancer have the best outlook, and the majority of the literature is on such patients; therefore, the discussion will be mainly concerned with colorectal liver metastases.

1.1. DETECTION OF LIVER METASTASES

1.1.1. BIOCHEMICAL TESTS
1.1.2. IMAGING
1.1.3. CONCLUSIONS

With major advances in the surgical and non-surgical treatment of liver metastases over the past decade, tumour detection has taken on great relevance in the management of these patients.

Patients presenting with symptoms of liver metastases usually have advanced disease, whereas those with solitary or several isolated hepatic metastases are usually asymptomatic. This latter group of patients are potentially curable and it is argued that early detection of recurrence in these patients allows more effective treatment (Martin et al, 1985), since they are at a more resectable stage (Ovasaka et al, 1990).

Hepatic metastases are said to be present in up to one third of patients undergoing apparently curative resection of their primary tumour (Greenway, 1988), many of which are not evident to the surgeon at the time of laparotomy (occult hepatic metastases) (Finlay and McArdle, 1986). The method of detection must maximise the sensitivity to these small metastases so that appropriate management decisions can be made.

The most important time for follow-up of patients is the first 2-3 years after resection of the primary cancer, since 85% of recurrences occur within this time (Kelly and Daly, 1992). This is carried out with clinical evaluation, laboratory tests and imaging.

1.1.1. BIOCHEMICAL TESTS

1.1.1.1. Liver function tests
Serum alkaline phosphatase (ALP) and lactate dehydrogenase are the most reliable liver function tests for detecting liver metastases, and significant elevations of these usually indicate extensive liver disease (Kemeny et al, 1986). However, they are often normal in the presence of small volume liver tumour, and also with extensive tumour infiltration.
(Kelly and Daly, 1992). Tartter et al (1981) evaluated ALP as a screening test for liver metastases in 327 patients with colorectal cancer; this was found to be elevated in 43 of the 56 patients subsequently established to have liver metastases (sensitivity 77%). However, ALP was also raised in 110 patients without metastases (false positive rate of 34%); thirteen patients with liver metastases had a normal ALP (false negative rate of 4%). Baden et al (1971) found neither ALP or gamma-glutamyl transpeptidase of any real predictive value as markers for liver metastases discovered at laparotomy.

These tests are of limited diagnostic value for the early detection of hepatic metastases.

1.1.1.2. Tumour markers

Carcinoembryonic antigen (CEA) is a glycoprotein which was first described in 1965 (Gold and Freedman, 1965) as a tumour marker for colorectal cancer, but has since been shown to be produced by other tumours, in non-malignant disorders, and by normal individuals (Northover, 1986). However, most interest has been in the role of CEA to detect recurrent colorectal cancer after removal of the primary. Northover (1986) performed a meta-analysis of six studies reported between 1982 and 1984. In a total of 2147 patients with colorectal cancer, 537 (25%) developed recurrent disease. Of these, 404 (75%) had an elevated CEA before or at the same time as the recurrence became clinically obvious. Of the patients that underwent laparotomy on the basis of a raised CEA, 85-90% had abdominal recurrent disease and most of the remainder were found to have extra-abdominal metastases within a year. Attiyeh and Stearns (1981) reported a resectability rate of recurrent disease of 43% of patients after a second-look laparotomy based on a raised CEA level. Similarly, Martin et al (1985) found a resectability rate of 58%, but also reported a 45% overall incidence of needless laparotomy in 145 patients.

The crucial question is whether a second-look laparotomy prompted by a raised CEA level after resection of the primary, improves overall survival or reduces morbidity. Two uncontrolled studies have reported overall improvements in survival rates of 2.5% (Scheissel et al, 1986) and 4% (Martin et al, 1985) following second-look operations based on a raised CEA level. However, randomised, controlled studies are needed and any survival improvement needs to be considered in the light of morbidity resulting from further major surgery, often in difficult circumstances (Lewis, 1988). Such a trial is currently being conducted in the UK, supported by the Cancer Research Campaign (Begent, 1992).

Measurement of serum CEA is relatively inexpensive and although not uniformly sensitive or specific, is a reliable marker of recurrent disease (Northover, 1986); regular measurements are useful since they are easily performed and can prompt further investigation if a rise occurs (Kelly and Daly, 1992).
Another tumour marker is carbohydrate antigen 19.9 (CA 19.9) which is primarily used in the diagnosis and management of pancreatic cancer. Raised levels of this marker have been found in 53-58% of patients with advanced colorectal cancer (Fillela et al, 1992), but it is not as sensitive as CEA for detecting recurrent disease (Szymendera et al, 1985).

The main limitation of biochemical indices in the detection of liver metastases is that they fail to provide the detailed anatomical information that is required when detecting early, small volume tumour, which is needed to allow adequate treatment planning. This requires some form of imaging.

1.1.2. IMAGING

Imaging plays a vital role in evaluating patients with liver metastases, in order to allow selection of candidates for hepatic resection or alternative therapy. Imaging should not only be able to detect tumour, but be able to characterise the size, number and segmental location of the lesions, and assess their relationship to the portal and hepatic veins and bile ducts. Imaging should also reliably detect extra-hepatic tumour, so that the incidence of unnecessary surgery is reduced (Balfe, 1992).

There has recently been a dramatic improvement in the imaging modalities available for liver tumour detection. The sensitivities of the different techniques have increased considerably, with nodules less than 1cm in size being frequently found (Ferrucci, 1990). However, despite the improvements, there is still no single imaging technique which is optimal for examination of potential surgical candidates.

There have been a large number of comparative studies performed, evaluating the relative sensitivity of different imaging techniques to detect liver metastases, but they all have the problem of choosing a reference gold standard. The ideal reference is pathological assessment, and although some studies do use this, it is confined to the resected specimen, making it impossible to be certain that the remaining liver is completely tumour-free. The surgeons hand at laparotomy can frequently miss tumours less than 2cm in diameter (Allen-Mersh, 1991), and Clarke et al (1989) found that 40% of lesions shown by intra-operative ultrasound were neither visible or palpable.

A description of the various imaging techniques is given below, followed by the results of some recent comparative studies.

1.1.2.1. Ultrasound (US)
The last decade has seen considerable improvements in ultrasound technology, with real-time scanning now being universally performed, and electronic focusing capabilities resulting in improved images and better resolution. Hepatic ultrasound is performed using...
a 3.5MHz or 5MHz transducer. Metastases may be hyperechoic, hypoechoic or of mixed echogenicity (Marn et al, 1991) and they often have a hypoechoic halo (Wernecke, 1992). Some metastases may appear only as an area of heterogeneity with poorly defined margins. In these cases, and in others where histological proof is needed, ultrasound can be used to guide needles for tissue biopsy allowing tumours as small as 5mm to be seen and targeted. One of the main advantages of ultrasound is to differentiate solid from cystic lesions, but it is not as helpful in distinguishing different causes of solid lesions.

Attempts are being made to improve the sensitivity of ultrasound examinations by using contrast agents such as perfluoro-chemicals (Behan, 1993) or carbon dioxide microbubbles (Kudo, 1992).

1.1.2.2. Computed tomography (CT)
CT plays a major role in the detection of liver metastases because of its high resolution images, short scan times and fast patient throughput. The contrast on a CT image depends on differences in tissue density. There are several technical parameters which need to be optimised when imaging liver tumours; these include the scanning time, slice thickness, slice spacing, and contrast agent (ie. type, volume, rate, and route of administration). The contrast used is iodine based and this increases the CT density (measured in Hounsfield units, HU) of perfused tissue; this allows improved detection of some liver lesions. Whether a tumour is seen on CT depends on the density difference between tumour and surrounding tissue, as well as the size of the tumour; for example, a 1mm calcified lesion may be easily seen, but tumours of several centimetres may not be visible if their density is only slightly different from adjacent tissue. However, CT will reveal the majority of liver metastases 1cm or larger.

Liver CT may be performed without contrast, following dynamic contrast enhancement, or 4-6 hours after contrast (delayed scans). On non-contrast scans, most hepatic neoplasms appear hypodense, but in the presence of liver steatosis they may be isodense or hyperdense (Ueda et al, 1988); calcification is often seen in colorectal liver metastases (Bernadino, 1979).

Dynamic contrast enhanced CT is performed during a bolus intra-venous injection of contrast (40-50g iodine) and rapid scanning (after a delay of 30-45 seconds) of the whole liver within 2-3 minutes (Foley, 1989). This technique gives high lesion-to-liver contrast, particularly of hypovascular tumours such as colorectal liver metastases, and it is estimated that the sensitivity of contrast enhanced CT is 10-15% higher than unenhanced CT (Nelson, 1991). There is very little agreement amongst Radiologists about the ideal type of contrast agent, optimal dose, rate of injection, or scan delay after injection (Dodd and Baron, 1993). Up to 39% of hyper-vascular metastases (eg. from an endocrine primary)
become iso-attenuating to normal liver after dynamic CT (Bressler et al, 1987), and in these cases a non-contrast CT or delayed CT is indicated.

Delayed CT scanning is useful in some patients, and is based on the fact that normal hepatocytes slowly excrete 1-2% of contrast agent (Chamberlain and Sherwood, 1966), and so normal liver will become hyper-attenuating relative to tumours (which do not contain functioning hepatocytes) usually 4-6 hours after contrast (40-60g iodine) administration (Bernadino et al, 1986).

Several hepatotropic contrast agents are being developed to improve the detection of liver metastases by CT. These include ethiodised oil emulsion (EOE-13) (Sugarbaker et al, 1984), perflubron emulsion (Behan et al, 1993), liposomes containing water soluble iodinated contrast agents (Musu et al, 1988), and polyiodinated triglycerides (Weichert et al, 1989); EOE-13 and perflubron emulsion do increase the conspicuity of liver metastases, but the former is not available commercially and the latter is limited by its side-effects (Miller et al, 1987; Behan et al, 1993). CT with iiodised poppyseed oil (Lipiodol) is very sensitive for detecting primary hepatocellular carcinomas and their intrahepatic metastases, but is not useful for showing the hypovascular metastases of colorectal cancer (Matsui et al, 1987). A recent major advance in CT is the advent of spiral CT (Bluemke and Fishman, 1993), which allows scanning of the whole liver within 24 seconds. More widespread use of this system will require re-evaluation of the parameters and techniques presently being used for liver CT.

1.1.2.3. CT Angiography

The blood supply to normal hepatic parenchyma is mainly from the portal vein, whereas the hepatic artery supplies most of the blood to liver tumours, primary or secondary (Breedis and Young, 1954; Taylor et al, 1979). This difference in predominant blood supply can be taken advantage of by selectively injecting contrast into either the hepatic artery (directly) or portal vein (indirectly), in order to maximise the enhancement difference between normal liver and hepatic tumours.

CT hepatic arteriography (CTHA) is performed by placing the tip of a 5F or 7F catheter into the hepatic artery (via the femoral artery), rapidly injecting contrast, and followed immediately by a dynamic incremental CT scan through the entire liver (Prando et al, 1979); tumours are seen as lesions with hyperattenuating rims (Moss et al, 1982).

CT arterial portography (CTAP) is performed by placing the catheter tip in the proximal superior mesenteric artery (SMA) or splenic artery. About 10s after starting a rapid contrast injection, a dynamic incremental CT scan of the liver is performed, the delay
allowing time for the contrast to pass from the SMA through the mesenteric capillary bed into the portal venous and eventually the hepatic venous systems (Nelson et al, 1989). Tumours are seen as hypoattenuating lesions, compared with marked enhancement of the surrounding hepatic parenchyma.

The choice between using CTHA or CTAP is often based on individual preference, but CTAP is the more popular technique (Harned et al, 1992), and it probably has fewer artefacts (Freeny and Marks, 1986) and slightly better sensitivity for detecting liver metastases (Lundstedt et al, 1986). CTAP can detect metastases 5mm in size, and sometimes smaller ones, although problems exist with misinterpretation of nodular perfusion defects (Nelson, 1991). Even so, CTAP is reported to be the most sensitive pre-operative imaging modality for hepatic lesion detection, particularly those less than 2cm in diameter (Harned et al, 1992); it also outlines the hepatic and portal venous structures very well.

1.1.2.4. Magnetic resonance imaging (MRI)

In MRI there at least ten tissue parameters which can influence the resultant image (Bydder, 1988); the most important of these are proton density, T1 and T2 relaxation times. The way in which these parameters influence the MR signal intensity is determined by the pulse sequence applied, the most frequently used being the spin echo, partial saturation and inversion recovery sequences; faster sequences include gradient echo and echo planar imaging. Pulse sequence parameters (such as repetition time, TR, and time to echo, TE) are crucial for determining tissue contrast, and altering them affects T1 and T2 dependent contrast; subsequent images may be T1 weighted (T1W) or T2 weighted (T2W). The quality of an MR image is determined by a variety of factors which include the tissue parameters, pulse sequence parameters, magnetic field strength, number of data acquisitions, and in abdominal imaging the reduction of motion artefact.

Hepatic metastases have longer T1 and T2 relaxation times compared to normal liver (Moss et al, 1984), and typically have a low signal intensity on T1W images and high signal intensity on T2W images. Some authors have described distinctive MR appearances of hepatic metastases, such as amorphous, target and halo signs on T2W images, and a doughnut sign on T1W images (Wittenberg et al, 1988); however, these appearances are only suggestive of metastases and not absolute indicators (Halvorsen and Thompson, 1991).

The optimal pulse sequence for the detection of hepatic metastases has been controversial (Kanzer and Weinreb, 1991). Some authors found a higher sensitivity with T1W spin echo sequences at low (0.6T) magnetic field strength (Henkelman et al, 1986), but at high field (1.5T) T2W sequences were better (Foley et al, 1987; Vassiliades et al, 1991). Others have found T1W and T2W sequences to be equivalent at 0.35T (Heiken et al,
1985; Schmidt et al, 1985). Paling et al (1988) showed a short inversion time inversion recovery (STIR) sequence to be most sensitive for metastatic disease at 1.0T. There are many more reports showing various sequences to be optimal at different magnetic field strength for detecting liver metastases, including gradient echo T2*W at 0.5T and 1.5T (Nelson et al, 1988), T1W spin echo at 0.5T (Reinig et al, 1989), T1W inversion recovery at 1.5T (Reinig et al, 1989), and equivalent sensitivities between T1W inversion recovery and T2W spin echo at both 0.5T and 1.5T (Steinberg et al, 1990).

The available data is contradictory. Valid comparison of two studies is almost impossible because of manufacturer and inter-machine variability, as well as different sequence parameters (TR and TE) being applied. The best solution is to use several sequences (T1W and T2W) to increase the confidence of detecting liver metastases.

Contrast agents are also available. Gadolinium DTPA is widely used; since this is an extracellular agent rapid imaging (using fast spin echo or gradient echo, breath-holding sequences) is needed to maximise the tumour-to-liver contrast (Hamm et al, 1987). This dynamic scanning may improve the sensitivity of MRI for liver tumour detection (Semelka et al, 1992). New hepatocyte specific and reticuloendothelial system targeted contrast agents are also being evaluated; these include manganese dipyridoxal diphosphate (MnDPDP) and superparamagnetic iron oxide, respectively, and early results look promising (Hamm et al, 1992; Ferrucci and Stark, 1990).

Liver tumours as small as 3mm can be detected with superparamagnetic oxide enhanced MRI (Stark et al, 1988). One of the drawbacks of MRI is that it is not very sensitive to extra-hepatic tumour, but with new oral contrast agents becoming available, this situation is likely to improve.

1.1.2.5. Intraoperative ultrasound (IOUS)

This technique has developed considerably over the past decade, with the development of real-time, high resolution scanners and hand held transducers (5-10MHz). Small transducers which can be held between the fingers to reach less accessible parts of the liver are also available (Rifkin et al, 1986).

Prior to metastectomy IOUS can show the size and extent of tumour, its depth from the liver surface, and any intervening or adjacent blood vessels, as well as any simultaneous minimal hepatic disease in the remaining hepatic parenchyma. Tumours as small as 3mm can be detected (Soyer et al, 1993).

IOUS can detect 25-35% additional liver lesions compared with preoperative ultrasound and CT, and up to 40% more lesions than are palpable by the surgeon (Clarke et al, 1989). Traynor et al (1988) found 13 out of 40 tumours less than 1cm in diameter by IOUS,
which had not been detected by preoperative imaging and were not palpable. Other surgeons have not found IOUS to detect any new metastases which were not palpable in a non-cirrhotic liver (Sugarbaker, 1990). Soyer et al (1992) using preoperative CTAP and IOUS found 3 out of 56 metastases by IOUS which were not seen on CTAP, and only 2 metastases missed by palpation. The high sensitivity of IOUS to small liver lesions means that benign nodules can often be found (Benjamin, 1991), which may require biopsy and histology before resection can proceed; this is ideally done with a sensitive preoperative technique (Sugarbaker, 1990). The use of IOUS necessitates a wide surgical exposure of the liver, and the technique is operator dependent.

1.1.2.6. Comparative studies of US, CT, CTAP, MRI, and IOUS

Although many authors have reported comparative imaging of liver tumours, these studies are often hampered by a small number of cases, different patient populations, considerable differences in technique used, inadequate pathologic proof, or researcher bias. These factors make comparison of reported differences in sensitivity very difficult (Dodd and Baron, 1993); for example, a subtle difference in the technique of contrast administration during dynamic CT could alter tumour detection rates by as much as 20% (Dodd and Baron, 1993).

Tables 1.1 and 1.2 show the sensitivities of the main imaging modalities found in recent comparative studies. Surgical or pathological proof was obtained in the majority of cases, but not all liver tumours were metastases. All CTs were contrast enhanced (dynamic or delayed), and the overall sensitivity of CT is given for each study. The MRI scans were usually obtained with several sequences, and the sensitivities given are the overall or best ones. Although the machines and techniques used do vary (sometimes considerably), the figures do represent what each modality is capable of at a particular institution (presumably using their preferred and locally optimised technique for CT and/or MRI).

In Table 1.1 there is a fairly wide discrepancy in the sensitivity of tumour detection for ultrasound (41-68%), CT (48-72%) and MRI (57-78%). One of the principle reasons is likely to be the various gold standards used in different studies. If pathologic specimens from liver resection or autopsy are used as the standard, many lesions smaller than 1-2cm could be found which were missed by imaging. However, if clinical follow-up or palpation during surgery is used, the sensitivities of most diagnostic tests will be higher because small lesions are unlikely to be included.

Ultrasound has the lowest sensitivity in these studies, but this modality is highly operator dependent and can often detect tumour not seen by CT. Ultrasound can also have a high false positive rate and the images are not easily reproducible for comparative purposes (Ferrucci, 1990). However, it is quick and easy to perform and is frequently used for initial assessment of liver metastases.
Table 1.1: Sensitivities of US, CT, MRI, CTAP, and IOUS for detecting liver tumours from 10 recent studies.

<table>
<thead>
<tr>
<th>First author, year</th>
<th>US</th>
<th>CT</th>
<th>MRI</th>
<th>CTAP</th>
<th>IOUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Machi, 1987</td>
<td>41%</td>
<td>48%</td>
<td></td>
<td></td>
<td>98%</td>
</tr>
<tr>
<td>Matsui, 1987</td>
<td>58%</td>
<td>63%</td>
<td>84%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stark, 1987</td>
<td>51%</td>
<td>64%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heiken, 1989</td>
<td>52%</td>
<td>57%</td>
<td>81%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nelson, 1989</td>
<td>66%</td>
<td>64%</td>
<td>85%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sitzman, 1990</td>
<td>66%</td>
<td>70%</td>
<td>94%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vassiliades, 1991</td>
<td>72%</td>
<td>78%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wernecke, 1991</td>
<td>53%</td>
<td>68%</td>
<td>63%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soyer, 1992</td>
<td>68%</td>
<td>71%</td>
<td>91%</td>
<td>96%</td>
<td></td>
</tr>
<tr>
<td>Soyer, 1993a</td>
<td>78%</td>
<td></td>
<td>94%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1.2: Sensitivities of US, CT, MRI, and CTAP for detecting liver tumours less than 1cm in diameter.

<table>
<thead>
<tr>
<th>First author, year</th>
<th>US</th>
<th>CT</th>
<th>MRI</th>
<th>CTAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heiken, 1989</td>
<td>0%</td>
<td></td>
<td>17%</td>
<td>61%</td>
</tr>
<tr>
<td>Sitzman, 1990</td>
<td>5%</td>
<td></td>
<td>20%</td>
<td>82%</td>
</tr>
<tr>
<td>Wernecke, 1991</td>
<td>20%</td>
<td>49%</td>
<td>31%</td>
<td></td>
</tr>
<tr>
<td>Soyer, 1993a</td>
<td></td>
<td></td>
<td>17%</td>
<td>66%</td>
</tr>
</tbody>
</table>

For more accurate staging of liver tumours, CT is performed. Although some studies have found MRI to be more sensitive than CT (Stark et al., 1987), the evidence is not conclusive, and for detection of extra-hepatic disease it is generally accepted that CT is better than MRI (Chezmar et al., 1988; Vassiliades et al., 1991; Halvorsen and Thompson, 1991). CT is also more readily available and cheaper than MRI, and is currently the preferred modality for liver imaging in the UK. Although some authors have reported a very high specificity (99%) for CT in detecting liver tumours (Ferrucci et al., 1988), this is not the case with solitary deposits when biopsy and histological confirmation of the diagnosis is frequently required (Halvorsen and Thompson, 1991).
CTAP has consistently been shown to be the most sensitive pre-operative imaging modality for detection of liver metastases (Balfe, 1992; Harned et al, 1992), especially for small tumours (Table 1.2). However, it is a more expensive, cumbersome and invasive technique, and has a significant false positive rate (Peterson et al, 1992). Combining CTAP with MRI reduces the false positive rate, and Nelson et al (1989) found a combined sensitivity of 96%. CTAP is particularly popular in the United States, and greater interest in this technique is being taken in the UK; a recent study has shown an improved survival in patients who have CTAP prior to hepatic resection (Langmo et al, 1992).

Two studies from the same centre (Miller et al, 1987; Ward et al, 1989) reported CTAP to be less sensitive than CT (77-78% versus 82-83%, respectively). However, their CTAP technique was flawed because they performed diagnostic angiography immediately prior to CTAP - this leads to contrast perfusing into the interstitial spaces of the tumour thus significantly reducing tumour-to-liver contrast during CTAP. For conventional CT they used a much higher dose of contrast (80-90g iodine) than is routine (40-60g), which may explain the high sensitivity of CT in their studies.

IOUS is very sensitive and can affect surgical decision making in several patients (Soyer et al, 1993). However, there is some debate over the overall utility of IOUS (Sugarbaker, 1990); it can be valuable in preventing some unnecessary hepatic resection (Benjamin, 1991), but has less impact when high quality preoperative imaging is available (Ferrucci, 1990).

Combining imaging modalities may improve the accuracy of tumour detection, and this has been shown to be the case for CTAP and MRI (Nelson et al, 1989). However, using combinations of US/CT, US/CT/MRI, and CT/MRI did not increase sensitivity beyond 80% (Nelson et al, 1989; Wemecke et al, 1991; Soyer et al, 1993).

1.1.2.7. Other imaging modalities

Radionuclide hepatic imaging
The liver-spleen technetium-99m sulphur colloid scan is now only rarely used for the detection of liver metastases (Drane, 1991). This decline is largely due to its inability to characterise a lesion - a "cold spot" on the scan may represent a solid or cystic lesion or an anatomical variant; the test also lacks spatial resolution and is less sensitive and specific than ultrasound and CT (Alderson et al, 1983). Single photon emission computed tomography (SPECT) improves tumour detection, and is said to have a sensitivity of around 90%, but its specificity is lower (Drane, 1991), and it is inferior to CT or MRI (Chamsangavej, 1993). Technetium-99m red cell scintigraphy is still useful in evaluating a solitary liver lesion, when the possibility of it being an haemangioma is high (Brown et al, 1987).
Hepatic arterial perfusion scintigraphy (HAPS) is a new method for early detection of liver metastases whereby technetium-99m-macroaggregated albumin is perfused into the hepatic artery, and tumours appear as hot spots on planar or SPECT scans (Drane, 1991). Tumour deposits as small as 5mm have been detected, and in one study a sensitivity of 91% was found, but the specificity was 50% because of hot spots from the gallbladder and duodenum (Fagien et al, 1990).

Dynamic hepatic scintigraphy has been used to determine the hepatic artery to total liver blood flow ratio, using activity-time curves from regions of interest over the liver (Leveson et al, 1983); early liver metastases cause an increase in hepatic arterial flow, and this is depicted by an increase in this ratio. Gough et al (1985) found that 50% of patients with colorectal cancer who had a raised ratio and initially normal liver scans, developed overt liver metastases within 6 months of follow-up.

Radioimmunoscintigraphy with monoclonal antibodies raised to CEA and labelled with I-131 or indium-111 allows gamma camera imaging, and can be useful in locating metastases (Begent et al, 1986) - this technique currently has a sensitivity of 45-64% for detecting liver metastases, but continues to develop (Norton, 1991). Radioimmuno-guided surgery using a hand held gamma probe to detect labelled I-125 antibodies (reacting with colorectal cancer antigens) has also been applied per-operatively to locate tumour (Blair et al, 1991). However, because of variable tumour vascularity and heterogeneous antigen expression, uptake of monoclonal antibody by tumour can be poor.

**Colour Doppler and duplex ultrasound**

This has been used to try to characterise liver tumours. Taylor et al (1987) found high velocity Doppler signals in primary hepatocellular carcinomas (due to arterioportal shunting) but low or absent signal in metastases or benign lesions. More recently, Nino-Murcia et al (1992) showed a considerable overlap between the internal vascularity of primary and secondary liver tumours.

Colour Doppler and duplex ultrasound has also been used to calculate the Doppler perfusion index (ratio of hepatic arterial to total liver blood flow); Leen et al (1993) found this to be significantly raised in patients with liver metastases compared to normal controls. This may be due to the fact that tumour blood supply is predominantly arterial, and so the presence of metastases would result in a relative increase of arterial blood flow; there may also be a circulating vasoactive agent causing an increase in splanchnic resistance with reduced portal venous flow and a relative increase in hepatic arterial blood flow.
Angiography

Diagnostic hepatic angiography has in general become an ancillary technique, its main role in liver metastases detection being in the catheter placement for CTAP (Ferrucci, 1990). As a diagnostic modality, it has a low sensitivity for liver metastases (Matsui et al, 1987), and consistently misses tumour in the left lobe of liver and extrahepatic tumour (Lundstedt et al, 1985). Prior to surgery, angiography is useful in providing a "road map" of arterial anatomy (Benjamin, 1991), and slightly delayed imaging allows visualisation of the portal vein.

1.1.3. CONCLUSIONS ON DETECTION OF LIVER METASTASES

Serum CEA level is a simple test to perform during follow-up of patients who have had their primary colorectal cancer resected, and many patients referred for hepatic resection are initially diagnosed as a result of abnormalities in CEA level (Sugarbaker, 1990). The widespread use of tumour markers and improvements in ultrasound, CT and MRI, as well as the development of CTAP and IOUS has markedly increased the detection of early small liver neoplasms.

However, there are no randomised prospective controlled studies to support the assumption that early detection and early treatment improve patient survival, and so the most important task of preoperative imaging prior to a planned liver resection is to prevent needless surgery. However, significant hepatic and extra-hepatic disease is still being missed. Extra-hepatic tumour presents a particular problem and currently, no preoperative imaging method is sensitive to small extrahepatic metastases, especially in hepatic lymph nodes and on the peritoneal surface (Balfe, 1992).

Significant improvements in the imaging are still needed, not only to accurately localise tumour deposits, but also to characterise them as benign or malignant, this being a particular problem with smaller nodules (Ferrucci, 1990).

The rapid pace of new developments requires continuous reassessment of the relative merits, clinical roles, and optimal techniques of the imaging modalities.

Standardisation of techniques and larger comparative studies are required; these should include combined state-of-the-art ultrasound and CT to compare with CTAP and MRI, since the former are still the simplest, cheapest and most widely available modalities for evaluating liver metastases.
1.2. NATURAL HISTORY OF LIVER METASTASES

1.2.1. GROWTH RATE
1.2.2. EXTENT OF LIVER TUMOUR
1.2.3. EXTRAHEPATIC TUMOUR
1.2.4. HISTOLOGY OF TUMOUR
1.2.5. CONCLUSIONS

A good understanding of the natural history of untreated liver metastases, and of the various factors which influence prognosis, is most important for appropriate patient management. This is needed to evaluate fully the significance of the many treatment modalities which are now available for patients with liver metastases, since it is impractical to have a no-treatment arm as a control in a clinical trial (Taylor, 1985); most patients would desire some form of treatment, even if unproven (Allen-Mersh, 1989). Our information on the natural history of liver metastases is largely based on earlier non-randomised, retrospective studies.

The overall prognosis for patients with liver metastases is dismal, regardless of the site of origin, with an average survival of approximately 6 months (Jaffe et al, 1968), and most patients dying within 2 years of diagnosis. However, there are several factors which determine the prognosis, and produce an extensive range of survival patterns, even up to 5 years from the time of diagnosis. These include the general condition of the patient, the extent of liver tumour present, the presence or absence of extra-hepatic tumour, and the histological grade of the metastasis. Symptomatic patients have a much worse prognosis than those without symptoms, the median survival being 6 months and 18 months, respectively (Steele and Ravikumar, 1989). The other prognostic factors listed are discussed below.

The observation that liver metastases from colorectal origin have a different natural history to those from other gastrointestinal neoplasms was made by Jaffe et al (1968), who found the median survival time of patients with liver secondaries from stomach cancer was 60 days, from biliary tract neoplasms 42 days, and from colorectal cancer 146 days. The mean survival times of patients with untreated liver metastases from pancreas and breast primaries is less than 8 months (Wolf et al, 1991). Neuro-endocrine liver metastases give a better prognosis since these tumours are relatively slow-growing; patients with untreated carcinoid liver metastases can have a 6 year survival rate of up to 25%, and those with pancreatic islet cell metastases have a median survival of 40 months (Wolf et al, 1991). Some patients with metastatic renal carcinoma can also have a relatively long survival if the metastases are limited to one organ and the disease free interval from diagnosis of the primary to detection of metastases is over 2 years (Maldazys and deKernion, 1986). Most data is on colorectal liver metastases, and this will now be discussed in more detail.
1.2.1. GROWTH RATE

Colorectal liver metastases tend to grow slowly and are said to be present for an average of 4 years before a patient's death (Finlay et al, 1988); a tumour of 2 cm will have had around 3 years of growth before being detected (Allen-Mersh, 1991). The doubling time for overt liver metastases is 5-6 months, and for occult metastases it is 3 months (Finlay et al, 1988). The growth rate declines with increasing tumour size (Laird, 1964). Dissemination to extra-hepatic sites such as lung and bone is often by secondary metastasis from metastases that have already developed in the liver (Weiss et al, 1986) - but this process may take several years (Allen-Mersh, 1991).

1.2.2. EXTENT OF LIVER TUMOUR

The overall survival of patients with colorectal liver metastases has been reported in several studies, which have been summarised by Hughes et al (1988), the median survival varying from 3 months to 14 months from the time the metastases are detected. The survival of patients in relation to the extent of tumour present in the liver has been described in several recent reviews (Taylor, 1985; Greenway, 1988; Hughes et al, 1988). The relevant data is summarised in Table 1.3. It is clear that survival is related to the extent of liver involvement by tumour. Hunt et al (1990) collated the survival data from 5 series and found a median survival of 21 months and a 3 year survival of 18% for solitary liver metastases; the corresponding figures for multiple metastases in one lobe of the liver were 14 months and 7%, respectively. Five year survivors are extremely rare; the 7% and 16% 5 year survival rates quoted in Table 1.3 by Wood (1976 and 1984) represents only 1 and 2 patients, respectively. Hughes et al (1988) reviewed 18 studies, and out of 1650 patients 11 survived 5 years (only 4 were histologically proven).

Table 1.3 highlights the lack of a well-defined and consistent method of describing the extent of the liver replaced by tumour; this makes valid comparison between one study and another very difficult. Simply describing the metastases as single, bilateral or multiple is inadequate, and a system which takes account of the volume of tumour present is preferable. The percentage hepatic replacement (PHR) is a more sensitive measure of tumour extent since it takes account of variation in liver size between patients. PHR can be assessed at laparotomy, or by imaging with scintigraphy, CT, or ultrasound (Hunt et al, 1989). However, there is considerable inter-observer variation when using these modalities for staging liver metastases into 4 broad groups of PHR, <25%, 25-50%, 50-75%, and >75% (Hunt et al, 1989). Purkiss and Williams (1992) found CT planimetry to be an accurate method of PHR assessment, using cadaver liver containing metastases. An inverse relationship between PHR and survival has been confirmed by several investigators (Purkiss and Williams, 1992; Finan et al, 1985). However, there is a need for an accurate and standardised methodology for measuring PHR.
Table 1.3: Survival of patients with untreated liver metastases. All of these studies are based on colorectal liver metastases except the one by Jaffe et al (1968) which includes pancreas, stomach and colon primaries.

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Tumour extent</th>
<th>Mean or median survival (months)</th>
<th>Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1yr</td>
<td>3yr</td>
</tr>
<tr>
<td>Jaffe, 1968</td>
<td>Solitary</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>One lobe</td>
<td>3.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Widespread</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td>Nielson, 1971</td>
<td>Few</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Several</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multiple</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Wood, 1976</td>
<td>Solitary</td>
<td>16.7</td>
<td>60%</td>
</tr>
<tr>
<td></td>
<td>One lobe</td>
<td>10.5</td>
<td>27%</td>
</tr>
<tr>
<td></td>
<td>Widespread</td>
<td>3.1</td>
<td></td>
</tr>
<tr>
<td>Bengtsson, 1981</td>
<td>&lt;25%</td>
<td>6.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>25-75%</td>
<td>5.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;75%</td>
<td>3.4</td>
<td></td>
</tr>
<tr>
<td>Boey, 1981</td>
<td>Unilobar</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bilobar</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Goslin, 1982</td>
<td>&lt;4</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;4</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Lahr, 1983</td>
<td>Unilobar</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bilobar</td>
<td>4.5</td>
<td></td>
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<tr>
<td>Wagner, 1984</td>
<td>Solitary</td>
<td>21</td>
<td>21%</td>
</tr>
<tr>
<td></td>
<td>Unilobar</td>
<td>15</td>
<td>6%</td>
</tr>
<tr>
<td></td>
<td>Widespread</td>
<td>10</td>
<td>4%</td>
</tr>
<tr>
<td>Wood, 1984</td>
<td>Solitary</td>
<td></td>
<td>21%</td>
</tr>
<tr>
<td></td>
<td>Unilobar</td>
<td></td>
<td>26%</td>
</tr>
<tr>
<td>Finan, 1985</td>
<td>Solitary</td>
<td>15.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multiple</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Steele, 1989</td>
<td>&lt;4</td>
<td>24</td>
<td>85%</td>
</tr>
<tr>
<td></td>
<td>&gt;4</td>
<td>10</td>
<td>40%</td>
</tr>
</tbody>
</table>
1.2.3. EXTRAHEPATIC TUMOUR

Surgery to the primary tumour not only provides palliation with relief of symptoms, but may also improve survival in patients with liver metastases. Abrams and Lerner (1971) found a median survival of 219 days in patients with liver metastases who had their primary resected compared with 65 days in patients who had a bypass or no procedure; Nielson et al (1971) and Oxley and Ellis (1969) also found improved survival in patients with liver metastases in whom the primary tumour was resected. However, these studies were not randomised, and it is likely that those patients with more advanced disease had the lesser surgical procedure. Finan et al (1985) showed that survival of patients with established liver metastases is related to the histological grade and stage of the primary; patients with a well or moderately differentiated primary had a median survival of 13 months compared to 7 months for those with a poorly differentiated primary, and the presence of affected lymph nodes reduced the median survival from 16.7 months to 10.8 months.

Patients who are found to have extrahepatic disease as well as liver metastases, following resection of the primary, also have a worse prognosis than those with liver metastases only; median survivals of 3 months and 6 months, respectively, have been reported by Purkiss and Williams (1992). Wood et al (1976) found patients with solitary liver metastases and extrahepatic disease to have a median survival of 16.7 months, whereas similar patients without extrahepatic disease had a median survival of 25 months.

1.2.4. HISTOLOGY OF TUMOUR

Pestana et al (1964) noted that patients with well-differentiated liver metastases had a survival of 11 months compared to 5.5 months for patients with poorly differentiated lesions. Goslin et al (1982) reported a median survival of 6 months in patients with poorly differentiated tumour, compared to 17 months and 30 months in patients with moderately and well differentiated metastases, respectively. However, the authors did not take into account the extent of liver tumour in their analyses.

1.2.5. CONCLUSIONS OF NATURAL HISTORY

The most important factor which influences survival in patients with untreated liver metastases is the extent of tumour in the liver. Other factors which are likely to affect survival are the extent of surgery to the primary tumour, the presence of extrahepatic tumour, and the histology of the metastasis.

Improvements in tumour detection by imaging means that greater numbers of patients with smaller volume disease are being found, at a much earlier stage. The survival of untreated
patients with early, small volume disease is likely to be better than reported in previous natural history studies. Silen (1989) postulated that if the mean age of overt metastases when detected is 3.7 years (Finlay et al, 1988), then the reported 5 year survival rates in the natural history studies actually correspond to a survival of about 9 years, with no treatment.

There is still much to learn about the natural course of liver metastases, and we have little understanding of the biological relationship which exists between the patient and the colorectal cancer. Some patients have a very rapid course between diagnosis and death with widespread metastatic disease consuming them, while others appear to form a sort of commensal relationship with their tumour and survive for a number of years.

When evaluating treatments it should be remembered that a large proportion of patients with relatively little liver involvement will bias any study favourably. All future treatment trials should stratify patients according to PHR; ideally an international standardised staging system should be used which categorises patients according to the major prognostic factors discussed above. This would allow more valid comparison of the results of different treatments.

1.3. TREATMENT OF LIVER METASTASES

1.3.1. SURGERY
1.3.2. SYSTEMIC CHEMOTHERAPY
1.3.3. REGIONAL TREATMENTS
1.3.4. LOCAL TREATMENTS
1.3.5. CONCLUSIONS

It is generally accepted that the majority of patients with liver metastases are not helped by currently available treatments. However, there is a group of patients, mainly with colorectal liver metastases, who have small volume tumour confined to the liver, which may be surgically resected and the patient potentially "cured". This number was estimated to be around 600 in 1989 (Allen-Mersh, 1989), but a more recent estimate is up to 2000 patients each year in the UK (Poston and Winstanley, 1992); Scheele (1993) suggested that 1-3% of all patients with colorectal cancer (28000 in the UK) may at some time benefit from hepatectomy. Since around 50% of patients with colorectal cancer develop liver metastases (Pickren et al, 1982), and 20% have tumour limited to the liver (Weiss et al, 1986), there remains a large number of patients with small volume tumour who are unsuitable for surgery and for whom an alternative effective treatment is needed. Many of these patients have a tumour volume significantly less than 25% PHR, but are unsuitable for surgery either because of several small deposits in different parts of the liver or the
tumours are very close to essential intrahepatic vascular structures. It is for these patients that some of the new regional and local treatment modalities may be particularly suitable, especially since the results of systemic chemotherapy have been disappointing.

Furthermore, far fewer than the estimated number of patients suitable for resection actually undergo surgery. In the UK, the traditional management of patients with liver metastases has emphasised the importance of maintaining quality of life; as a result it has been common for no treatment to be given prior to the development of symptoms, and thereafter only symptom relieving treatment to be given a trial. This approach has been based on the view that available treatments have virtually no effect on survival, and since hepatic metastases may be asymptomatic and slow growing, it is preferable to avoid subjecting the patient to treatment-induced morbidity (Hunt et al, 1990).

1.3.1. SURGERY

The selection criteria for surgical resection have changed over the past 20 years, but still remain controversial. The general consensus appears to be that resection is the treatment of choice for up to 3 colorectal liver metastases confined to one lobe and in the absence of extra-hepatic disease, assuming that satisfactory surgical margins can be achieved (Scheele, 1993; Taylor, 1992).

The majority of the literature deals with colorectal liver metastases, and reports of surgery for non-colorectal metastases are sparse and inconsistent. Wolf et al (1991) reviewed the literature on 151 reported cases; favourable results were obtained after resecting metastases from Wilms' tumour or carcinoid (40% 5 year survival). Anecdotal reports of long term survival after hepatic resection of metastases were also found in patients with renal, adrenal, gastric and breast primaries, as well as malignant melanoma and leiomyosarcoma. Blumgart and Studley (1988) suggest that resection of solitary metastases from unfavourable primaries should be considered, if a low operative mortality can be maintained; the likelihood of therapeutic benefit may be so marginal that more than a single metastases should not be resected (Scheele, 1993). Endocrine metastases, such as carcinoid, islet cell carcinoma and gastrinoma, may grow extremely slowly, patients sometimes surviving up to 10 years without treatment (Scheele, 1993). Debulking these tumours by surgery or embolization can significantly improve symptoms and quality of life (Allison et al, 1985; Modlin et al, 1993).

Operative mortality ranges from 0% to 14% (Iwatsuki et al, 1983; Hunt et al, 1990; Petrelli et al, 1985), although over the last 5 years this has been commonly reported to be 5% or less (Steele and Ravikumar, 1989; Franco, 1991). Minor and/or major morbidity has been reported in 10% to 48% of patients (Gennari et al, 1986; Vetto et al, 1990), but with improvements in surgical technique this is also decreasing (van Ooijen et al, 1992).
Scheele et al (1991) found a decrease in mortality and morbidity over the most recent 2 years of their series, from 11.5% and 22% to 2.7% and 8%, respectively.

1.3.1.1. Survival after surgery
There are numerous reports in the literature of results of surgical resection in selected patients with colorectal liver metastases, and Table 1.4 summarises some of these.

Comparing this data with the natural history data in Table 1.3, there is little difference in the 1 year survival when considering single metastases, but at 3 years and 5 years the results following surgery appear considerably better than the natural history data. Many 5 year disease-free survivors may be regarded as "cured" (Scheele, 1993), and several patients have been reported to have survived for more than 20 years after surgery (Scheele et al, 1990; Adson, 1981; Butler et al, 1986). However, one of the difficulties of comparing this data with the natural history data is that the latter is likely to include many unresectable patients, and the surgical patients are highly selected. In order to determine whether a patient really benefits from surgical resection of their liver metastases, a randomised comparison is needed with similar patients who are left untreated or receive medical treatment; no such trials are available and so reliance has to be put on historical controls.

Steele et al (1991) performed a prospective evaluation of patients presenting for resection of their colorectal liver metastases; 150 patients had a laparotomy with a view to resection. Sixty nine (46%) patients had a "curative" resection and their median survival was 37 months, whereas 18 (12%) patients who had a "non-curative" resection had a significantly shorter survival of 21 months. The other 63 patients (42%) were found to be unresectable yet still had a median survival of 16.5 months. They concluded that resection does improve survival in a selected group of patients, but "palliative" resection or "debulking" in asymptomatic patients provides no benefit. Similar conclusions were drawn by Scheele et al (1990). Out of 921 patients with unresectable liver metastases, the median survival was 6.9 months; 62 patients had demonstrable resectable disease at laparotomy but this was not treated because of the different therapeutic approach at the time, and their median survival was 14.2 months. Of 226 patients who had a resection, in 43 this was non-radical and some tumour was left behind; these patients had a median survival of 13.3 months. In none of these groups were there any 5 year survivors, but of the 183 patients who had a potentially curative resection, the 5 and 10 year actuarial survival rates were 40% and 27%, respectively.
### Table 1.4: Survival rate after resection of colorectal hepatic metastases

<table>
<thead>
<tr>
<th>First author, year</th>
<th>No. of patients</th>
<th>Median (months)</th>
<th>Actuarial (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1yr</td>
<td>3yr</td>
</tr>
<tr>
<td>Attiyeh, 1978</td>
<td>25</td>
<td>40</td>
<td>28</td>
</tr>
<tr>
<td>Wanebo, 1978</td>
<td>25</td>
<td>36</td>
<td>92</td>
</tr>
<tr>
<td>Rajpal, 1982</td>
<td>30</td>
<td>31</td>
<td>85</td>
</tr>
<tr>
<td>Iwatsuki, 1983</td>
<td>24</td>
<td>91</td>
<td>73</td>
</tr>
<tr>
<td>Fortner, 1984</td>
<td>65</td>
<td>89</td>
<td>57</td>
</tr>
<tr>
<td>Adson, 1984</td>
<td>141</td>
<td>70</td>
<td>40</td>
</tr>
<tr>
<td>Butler, 1986</td>
<td>62</td>
<td>36</td>
<td>50</td>
</tr>
<tr>
<td>Ekberg, 1986</td>
<td>72</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Hughes, 1986</td>
<td>607</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scheele, 1991</td>
<td>266</td>
<td></td>
<td>41</td>
</tr>
<tr>
<td>van Ooijen, 1992</td>
<td>118</td>
<td>26</td>
<td></td>
</tr>
</tbody>
</table>

1.3.1.2. Factors influencing outcome after surgery

Factors which determine survival or recurrence following resection have been evaluated in several series, although conflicting results have been published for most of these. Those that probably have no significant effect on long-term survival include the patient's age and sex, size and location of the tumour, and type of resection (van Ooijen et al, 1992; Benjamin, 1991; Franco, 1991).

Most series have shown an improved survival of patients who have had smaller volume of liver tumour resected; Hunt et al (1990) combined the data from several studies and found the median survival of patients with solitary metastases resected to be 36 months, compared with 23 months for those who had multiple metastases resected. Ekberg et al
(1986) found a 5 year survival of 24% after surgery in patients with a PHR <25%, 7% with a PHR of 25-50%, and 0% with a PHR of 50-75%. Several groups have found impaired survival in patients with 4 or more metastases resected, and it is widely felt that patients with more than 3 metastases should not have surgical resection (Hughes et al, 1988; Taylor, 1992; Benotti and Steele, 1992; van Ooijen et al, 1992). However, some authors have reported long-term survival following resection of 4 to 7 metastases (Nordlinger et al, 1987; Scheele et al 1991), and in one case up to 13 nodules (Minton et al, 1989).

The presence of extrahepatic metastases, whether nodal or visceral, is consistently associated with poor survival (Hughes et al, 1988; Scheele et al, 1991) and resection in these cases is rarely indicated (Benjamin, 1991).

A resection margin of at least 1cm clear of tumour is associated with a much improved survival (van Ooijen et al, 1992; Ekberg et al, 1986; Cady et al, 1992). Scheele (1993) recommends margins of 1.5-2cm in the non-cirrhotic patient, unless more than half of the hepatic parenchyma would need to be removed.

The Dukes' stage of the primary tumour has been shown in several studies to have a significant effect on survival, a Dukes' C primary being a bad prognostic indicator compared to Dukes' A or B (Attiyeh et al, 1978; Adson et al, 1984; Butler et al, 1986). Others have found no significant effect of the stage of the primary on patient survival (Petrelli et al, 1985; Ekberg et al, 1986; van Ooijen et al, 1992). However, it seems reasonable to assume that the long-term prognosis is related to the stage of the primary, and is poor when there is lymph node or peritoneal involvement (Franco, 1991).

Other factors which are associated with a poor prognosis include the presence of satellite nodules (Scheele et al, 1990), per-operative blood loss greater than 1000ml (van Ooijen et al, 1992), and a disease-free interval (from original surgery to detection of metastases) of less than one year (Hughes et al, 1988).

The most important factors determining outcome after surgery are the presence of extrahepatic disease, the extent of liver involvement, and the resection margin; these need careful evaluation, ideally with pre-operative imaging, and also at operation - the use of intra-operative ultrasound may help in attaining tumour-free margins.

1.3.1.3. Recurrence after surgery
The majority of patients having surgical resection of their liver metastases will suffer a tumour relapse, the liver being the predominant site (Scheele, 1993). Most patients will die within 3 years, and 75% will die of recurrent disease within 5 years (Greenway, 1988). Recurrence tends to occur within a year to 18 months of surgery, and it is likely
that it is due to micrometastases which were not detected at operation or by pre-operative imaging.

Most authors report a 35-60% recurrence rate over a variable period of follow-up (Hunt et al, 1990), and there is a high incidence of extra-hepatic recurrence (Greenway, 1988). Hughes et al (1986) collected the data from 24 centres, and out of 607 patients who had had a "curative" resection, recurrent tumour was found in 424 (70%) patients; the liver was involved in 242 (43%) patients. Therefore, 57% of patients did not have recurrent disease affecting the liver, and Hughes et al concluded that hepatic resection has taken a group of patients all of whom had hepatic metastases and achieved complete control of liver tumour in about half of them.

Recurrent tumour isolated to the liver occurs in 10-55% of cases (Vaillant et al, 1993), and in a small number of these, resection of the recurrence may be appropriate (Bozzetti et al, 1992; Vaillant et al, 1993).

Because of the high rate of recurrence, most surgeons assess the biological behaviour of metastases by waiting a few months before resection, especially for small lesions (Scheele, 1993). This allows micrometastases to be detected before undertaking a possibly unnecessary major procedure. The argument against waiting is that it may increase the risk of further tumour embolization (Greenway, 1988). Some surgeons recommend a routine waiting period of 4-6 months (Cady and Stone, 1991), others 3 months (Benjamin, 1991; Scheele, 1993); however, a lesion of 5-6cm at first recognition is usually removed without a delay (Scheele, 1993).

1.3.1.4. Conclusions of surgical treatment
Surgical resection of liver metastases can, in selected patients, produce impressive 5 year survival rates (25-40%) with a low operative mortality, and this has been confirmed in most of the reported surgical series. Despite having a significant morbidity and high recurrence rate, surgery is the only treatment which offers the chance of a cure in some patients; even though this number is small, surgery does have an important role in the management of patients with liver metastases, and should be offered to selected patients (Taylor, 1992). Tumour biology needs to be better understood to aid in selecting appropriate patients. Effective medical treatment is also urgently needed, not only to reduce recurrence after surgery, but also to give some hope to the large number of patients for whom surgery is inappropriate.

1.3.2. SYSTEMIC CHEMOTHERAPY

Most patients with colorectal liver metastases receive treatment with systemic chemotherapy, and so this has been the focus of considerable attention. However,
progress has been slow and the results disappointing; complete responses are rare, and partial responses generally are reported in fewer than 25% of affected patients (Mayer, 1992).

1.3.2.1. Single agent chemotherapy

Since its introduction into clinical trials more than 30 years ago, 5-fluorouracil (5-FU) remains the most effective single agent. A review of the literature of more than 2000 cases of metastatic colorectal cancers treated with 5-FU by various schedules found a response rate of only 21% (Carter and Friedman, 1974). The response duration is only 3-6 months, and the majority of patients will not survive a year (Thompson and Wrigley, 1988). Parenteral 5-FU has been shown to be more effective than the oral form (Hahn et al, 1975), and low dose continuous infusion produces a greater response than a standard bolus schedule (30% versus 7%) but with no improvement in overall survival (Lokich et al, 1989). The reported survival times from studies using single agent 5-FU range from 7 to 13 months (Mayer, 1992). Toxicity can be a particular problem and includes bone marrow suppression, diarrhoea, and mucositis. 5-FU alone is not considered to improve median survival, although a controlled trial against no chemotherapy has never been performed.

Many other single agents have been tried in advanced colorectal cancer, the majority of which are ineffective (Mayer, 1992). Similarly, recombinant biotherapeutic agents such as the interferons, human tumour necrosis factor, and interleukin-2 have not been shown to be effective (Mayer, 1992).

1.3.2.2. Combination chemotherapy

Attempts to combine various chemotherapeutic agents with 5-FU have failed to consistently improve response rates over 5-FU alone, largely because of the dose reductions needed to prevent additive toxicities (Herrmann, 1993). Although there was initial enthusiasm with combinations such as semustine, vincristine, streptozotocin and 5-FU, with partial responses in more than 30% of patients (Kemeny et al, 1983), other studies showed similar response rates and median survival times with 5-FU alone (Richards et al, 1986). More recently, several prospective studies have compared cisplatin and 5-FU with 5-FU alone; no improvement in median survival time was found with the combination, and the cisplatin gave rise to significant toxicity (Mayer, 1992). The combination of 5-FU and levamisole has also generated interest, since this has been found to reduce the recurrence rate and prolong survival in patients with Dukes' stage C colorectal carcinoma, when used as adjuvant therapy (Moertel et al, 1990). However, for treating advanced colorectal cancer, this combination was no better than 5-FU alone in terms of response rates and median survival times (Buroker et al, 1985).
1.3.2.3. Biochemical modulation of 5-FU
This involves the use of a pharmacologic agent to increase the biologic effect of a second drug; in this context, such agents include allopurinol, methotrexate, PALA (phosphonacetyl-L-aspartate), interferon, and folinic acid (Kemeny et al, 1993). Allopurinol has been abandoned because of CNS toxicity and failure to improve clinical results (Herrmann, 1993). With methotrexate the results have been conflicting, and despite 10 years of clinical trials, it is still uncertain whether the methotrexate and 5-FU combination is superior to 5-FU alone (Mayer, 1992). Two recent uncontrolled studies showed an objective response in 42% of patients given PALA and a low dose infusion of 5-FU (Ardalan et al, 1988; O'Dwyer et al, 1990); this encouraging data warrants further investigation. In an initial report of interferon plus 5-FU, there was a 63% response rate (Wadler et al, 1990); however, two other reports, using the same dose and schedules, yielded only a 24% response rate with significant toxicity in one (Kemeny et al, 1990), and a 35% response rate in the second study (Pazdur et al, 1990).

The most successful method of modulating the cytotoxicity of 5-FU has been to combine it with folinic acid (leucovorin). Various schedules of folinic acid and 5-FU have yielded response rates of 15-45% in previously untreated patients with metastatic colorectal cancer, which on average are considerably higher than what is to be expected from 5-FU alone (Herrman, 1993). The results of several randomised studies have confirmed the better response rate of folinic acid and 5-FU over 5-FU alone (Arbuck, 1989); the doses and schedules of both drugs varied greatly and have not yet been optimised. In two of these trials there was a significant improvement in median survival, from 7 months to 12 months (Poon et al, 1989; Ehrlichman et al, 1988); however, for one of these, this claim has been withdrawn after longer follow-up (Ehrlichman, 1991). A recent meta-analysis of most of the reported studies has concluded that overall survival is not improved by the use of folinic acid and 5-FU compared with 5-FU alone (Advanced Colorectal Cancer Meta-Analysis Project, 1992). While overall responses are more frequent with the combination, this advantage is lost for studies that used a high dose intensity of 5-FU in their control arm (Valone et al, 1989). The addition of folinic acid appears to markedly increase the degree of gastrointestinal toxicity (Grem et al, 1987).

After all these studies the oncology community is not unanimous about the use of folinic acid and 5-FU. While some are claiming this combination to be the new standard, others tend to be less convinced. Even so, this combination is currently the most widely used initial form of treatment for patients with advanced colorectal cancer (Rubens et al, 1992); the best results in terms of response, quality of life, and survival have been reported by Poon et al (1989), and since their regimen is fairly easy to manage and not too expensive it has gained the most popularity (Herrmann, 1993).
1.3.2.4. Conclusions of systemic chemotherapy
Although systemic chemotherapy for advanced colorectal cancer has improved over the past decade, with increased response rates, the impact on survival has been minimal, and toxicity remains a significant problem. Many studies do not clarify how often the liver is the predominant area under study as opposed to other sites of metastases, which makes interpretation with respect to liver metastases difficult.

A recent study from the Nordic Gastrointestinal Tumour Adjuvant Therapy Group (1992) showed that early chemotherapy in patients with asymptomatic advanced colorectal cancer improved median survival by 5 months (p<0.01) and symptom free period by 6 months (p<0.001), as opposed to giving chemotherapy only after development of symptoms. Scheithauer et al (1993) performed a randomised comparison in patients with advanced colorectal cancer, of chemotherapy (5-FU+leucovorin+cisplatin) and supportive care versus supportive care alone. Although the numbers were small, overall survival was significantly longer for patients given chemotherapy (11 months) than for those receiving supportive care alone (5 months; p=0.006). There was no significant difference between the 2 groups in quality of life scores, and in those patients with abnormal scores before treatment, quality of life seemed better in the chemotherapy arm. These studies, if confirmed, could justify the case for careful follow-up of patients after resection of their primary and use of chemotherapy as soon as recurrence is detected.

One area which shows promise is surgical adjuvant chemotherapy to reduce the incidence of recurrence after resection of the primary. Given systemically to patients with Dukes stage C colon cancer, 5-FU and levamisole have been shown to reduce the recurrence rate by 41% (p<0.00005) and the death rate by 33% (p=0.0052) at a median follow-up time of 3 years (Moertel, 1992); although this has been recommended as routine therapy for Dukes C cancers by the National Cancer Institute in the USA, many clinicians in the UK remain sceptical and await the results of further randomised trials (Consensus on adjuvant treatment of colorectal cancer, British Institute of Radiology Conference, Glasgow, May 1993). Taylor et al (1985) in a randomised, prospective study, found a significant reduction in the incidence of liver metastases and an improvement in survival in patients receiving 5-FU infusion into the portal vein at the time of surgery to the primary; this was not confirmed by Beart et al (1990) in a similar study. The UKCCCR are currently performing a large randomised study to clarify the role of intra-portal 5-FU infusion for the prevention of hepatic metastases, and this forms part of the AXIS trial (Gray et al, 1991).
1.3.3. REGIONAL TREATMENTS

The very limited benefit from systemic chemotherapy has stimulated attempts at regional treatments to the liver for metastatic disease, since in a large number of patients the tumour is confined to the liver.

1.3.3.1. Regional chemotherapy

This is administered via the hepatic artery, since liver metastases derive the majority of their blood supply from the hepatic artery (Breedis and Young, 1954; Taylor et al, 1979). Metabolism of 5-FU or floxuridine (FUDR) by the liver allows maximal effect to the tumour and reduces systemic toxicity (Ensminger et al, 1978). Earlier, uncontrolled studies showed very good partial responses, up to 83% (Niederhuber et al, 1984). The results of several randomised trials comparing hepatic arterial infusion of FUDR with systemic therapy (5-FU or FUDR) are now available. They all show significantly improved hepatic response rates in patients receiving intra-arterial therapy (response rates 42-62%) compared with those receiving systemic treatment (response rates 10-21%) (Ensminger, 1993). The patients who received regional therapy had a 1-6 month improvement in median survival, but this was statistically significant in only one trial (Rougier et al, 1992). The toxicity with intra-arterial therapy was significant; 50% of patients in one trial had biliary cirrhosis, and chemical hepatitis occurred in 42% of patients in one study and 79% of patients in another (Mayer, 1992).

It is generally accepted that regional chemotherapy improves the response rate of liver metastases compared to systemic therapy, but there is disagreement on whether the former improves survival, particularly with the responses currently being obtained from systemic 5-FU plus folinic acid (Kemeny, 1992; O'Connell, 1992). However, to date, no controlled trial has convincingly shown improved survival rates with regional rather than systemic therapy (Pentecost, 1993). A major problem with regional therapy is the progression of extra-hepatic disease which the majority of patients eventually succumb to (Allen-Mersh, 1989), and a combined regimen of regional and systemic chemotherapy may have a role (Safi et al, 1989).

1.3.3.2. Ischaemic therapies

Because the predominant blood supply of liver tumours is from the hepatic artery, attempts have been made to restrict the blood flow to these tumours, the objective being to reduce tumour mass and improve survival. Hepatic artery ligation or dearterialization on their own have no survival benefit in patients with liver metastases (Bengmark and Jeppsson, 1989), the latter also being associated with significant morbidity and mortality (Almersjo et al, 1972). However, repeated transient dearterialization with an inflatable balloon in the hepatic artery can improve symptoms in patients with carcinoid liver metastases (Persson et al, 1989).
Taylor (1978) combined hepatic artery ligation with distal artery infusion of 5-FU with or without portal vein infusion of 5-FU, in a randomised, controlled study. He found no survival benefit of hepatic artery ligation and intra-arterial 5-FU over untreated controls; however, combined with portal vein infusion, the survival improved significantly, from a median of 3 months to 9.8 months (although numbers were small). Ekberg et al (1986a) found no survival improvement in patients receiving temporary dearterialization plus intra-arterial 5-FU over those receiving 5-FU alone. Gerard et al (1986) reported no survival benefit of hepatic artery ligation and portal vein infusion of 5-FU compared to hepatic artery ligation alone, both groups having a median survival of 11 months. Laufman et al (1984) found a 63% response rate and a median survival of 13 months in 19 patients with colorectal liver metastases treated by hepatic artery ligation and portal vein infusion of 5-FU and mitomycin C. These studies do suggest that delivering chemotherapy via both the hepatic artery and portal vein gives better responses than either alone, indicating that the portal vein supply of metastases, although limited, is of importance (Lin et al, 1984; Taniguchi et al, 1993).

Hepatic artery embolization performed under radiological control is an alternative method of occluding hepatic arterial flow, which may improve symptoms in patients with endocrine metastases (Allison et al, 1985) and in some patients with colorectal liver metastases (Taylor, 1985). Chuang and Wallace (1981) obtained promising survival results with this technique, but Hunt et al (1990a) in a randomised trial, found no survival benefit from embolization of colorectal liver metastases compared with untreated controls.

Embolization has also been performed with hepatic arterial infusion of cytotoxic agents, with variable results, and no convincing survival benefit (Okamura et al, 1982; Patt et al, 1983; Shimamura et al, 1988). Chemoenbolization has also been performed for liver metastases, by attaching drugs to microspheres prior to delivery via the hepatic artery. Small metastases capture these microspheres in preference to normal liver because they have a relatively greater blood flow; use of degradable material such as starch microspheres allows repeated treatments. Encouraging results have been reported by Hunt et al (1990a); they found an improved survival in patients receiving intra-arterial 5-FU and starch microspheres compared to untreated controls (median survival 9.6 versus 13 months, respectively), but this was not statistically significant, which may have been due to the small patient numbers.

1.3.3.3. Radiation therapies
This can be delivered as external beam therapy or by injection of radioactive substances. External beam radiotherapy for liver metastases is limited by the radiosensitivity of normal liver; the maximum dose which can be given without a high probability of inducing radiation hepatitis is 35Gy (Thomas, 1984). This does not influence survival (Taylor, 1985), although it may palliate symptoms such as pain, nausea and fever (Borgelt et al,
Combined radiotherapy and regional chemotherapy (FUDR or 5-FU) has been used by several investigators, but the average response rate is no higher than regional chemotherapy alone, and toxicity may increase (Kemeny and Sugarbaker, 1989).

Several studies have reported injection of yttrium-90 microspheres into the hepatic artery, with good objective reduction of tumour volume (Grady, 1979; Gray et al, 1992); however, the morbidity can be significant (Novell et al, 1991), and a survival benefit has not been shown. Ariel and Padula (1978) combined intra-arterial radiation with 5-FU, and found a 60% improvement in symptoms and mean survival times of 12-14 months in 65 symptomatic patients with liver metastases. Lipiodol (labelled with I-131) may also be used as a vehicle for selective internal radiotherapy of liver tumours, although localisation of lipiodol in large colorectal liver metastases is very poor (Hind et al, 1991).

I-131 labelled anti-CEA monoclonal antibody has been described for treating colorectal liver metastases (Delaloye et al, 1985), but the delivery of a lethal radiation dose to tumour cells is not yet within the scope of monoclonal techniques (Novell et al, 1991), and toxicity remains a significant problem (Beatty, 1992). Uptake of monoclonal antibody by tumour is poor because of variable tumour vascularity and heterogeneous antigen expression.

1.3.3.4. Conclusions of regional therapies

Hepatic arterial chemotherapy is at an impasse, with an inability to conclude whether the benefits outweigh the risks (Ensminger, 1993); technical progress and improved regimens are needed, although, if a more effective systemic therapy is found, regional therapy alone may have little to offer. Combining ischaemic therapies with regional chemotherapy may have a useful role in the future, particularly with repeatable therapy using degradable starch microspheres. Irradiation, either internal or external, may be valuable in palliation of severe pain, but there is no convincing evidence that overall survival is improved at a dose which can be safely delivered to the liver.

Overall, regional therapies require further improvements, and controlled trials are needed to show any worthwhile benefit; the likelihood of extra-hepatic disease remains high, even in patients whose disease appears macroscopically confined to the liver.

1.3.4. LOCAL TREATMENTS

Since the results of systemic and regional therapies have been generally poor, and surgery is appropriate in only a small number of patients, there has been considerable interest recently in different ways of locally destroying liver tumours. The main objective is to destroy liver metastases completely, while keeping morbidity to a minimum. The rationale is that effective in situ destruction of tumour plus a margin of surrounding normal liver
may provide a survival benefit, if applied to a similar group of patients who benefit from surgical resection. Furthermore, local therapy could also be used to treat a much larger group of patients who have small volume tumour confined to the liver, but do not fit the criteria for surgery. These local therapies are described below; all are either minimally invasive or non-invasive, apart from cryotherapy which requires a laparotomy.

1.3.4.1. Cryotherapy
This involves freezing tumours by cryoprobes, and is the most invasive local therapy since it requires a laparotomy. Using intra-operative ultrasound (IOUS) guidance, 3-8mm cryoprobes are inserted into the tumour, and freezing accomplished by circulating liquid nitrogen at -196°C through the inside of the probe (Bayjoo and Jacob, 1992). The volume of tumour destroyed can be accurately assessed by IOUS and is seen as an enlarging echogenic "iceball" (Onik et al, 1986); a 3cm iceball is produced by an 8mm cryoprobe (Bayjoo and Jacob, 1992). Charnley et al (1989) reported 7 patients with 39 liver metastases (size 0.5-6.5cm) treated by cryosurgery; CT scanning of all lesions after treatment showed evidence of tumour necrosis and regression in size at 6 weeks, and CEA levels fell in 3 patients, although no survival data was available. Ravikumar et al (1991) treated 24 patients with colorectal liver metastases, and at a median follow-up of 2 years (range 5 months to 5 years), 7 (29%) were disease-free, 8 (33%) were alive with tumour recurrence, and 9 (38%) had died. In only 2 (8%) patients, recurrence was noted at the cryo-ablated site in the liver. In an earlier study of 20 patients, Ravikumar and Steele (1989) reported a 3 year disease-free survival of 25%. From the published studies, smaller tumours (less than 4cm) appear to respond well, and survival data from these uncontrolled early studies looks promising (Bayjoo and Jacob, 1992).

Cryosurgery has low morbidity and no operative mortality has been reported. Complications include asymptomatic pleural effusions, bleeding after "freeze-thaw" cracking of the liver surface, myoglobinuria, and hepatic abscess (Bayjoo and Jacob, 1992).

Modern technology has allowed cryotherapy to evolve as a feasible and relatively safe technique for destroying small liver tumours. The main disadvantage is that it requires a laparotomy with its associated morbidity and limitation of repeatability for recurrent tumour. An advantage of performing a laparotomy is that it permits the use of IOUS, which improves tumour detection and allows accurate targeting of the tumour.

1.3.4.2. High intensity focused ultrasound (HIFU)
In this technique, ultrasonic energy of frequency 1-7.5MHz is generated in an external transducer, and brought to a sharp focus at a pre-determined depth within the body. With high intensity (>100W/cm²) ultrasound there is rapid tissue destruction in the focal zone (within 1 second), and the local temperature rises up to 120°C in vivo (Vallencien et al,
1992). Focal coagulative necrosis is produced by a combination of cavitation and thermal effects (Vallencien et al, 1991), and experimental work in animal liver and tumour models has demonstrated that well-defined zones of coagulative necrosis can be safely and reproducibly induced (Chapelon et al, 1992; Yang et al, 1992; ter Haar et al, 1991).

Clinical experience is currently very limited. Vallencien et al (1992) treated 2 patients with solitary liver metastases prior to surgical resection. In one patient there was no effect seen, which was attributed to an error in the composition of the coupling fluid; in the other patient there was enormous laceration of the tissues and patchy areas of necrosis within the tumour which may have been spontaneous and unrelated to HIFU. One of these patients also received a third degree skin burn.

Although the concept of HIFU is attractive, with the potential of non-invasively ablating liver tumours, considerable improvements are still needed in the technique. Intervening subcutaneous fat, bone, lung or bowel may considerably attenuate the ultrasound beam, and movement of the liver due to respiratory excursion may severely aggravate targeting difficulties.

1.3.4.3. Percutaneous alcohol injection
This is performed under ultrasound guidance, 1-8mls of sterile absolute (95-99%) alcohol being injected through thin (22 gauge) needles directly into liver tumours (Livraghi et al, 1992; Shiina et al, 1993). The exact quantity of alcohol used is not precisely defined, and depends to some extent on the size of the tumour and response after initial therapy; injection of 10-20mls three times weekly for up to 12 treatments is common (Dusheiko et al, 1992). Alcohol exerts its cytotoxic effect by a direct action, causing cellular dehydration and coagulative necrosis (Van Eyken et al, 1991). Most experience of this technique has been reported in patients with small hepatocellular carcinomas, largely by Italian and Japanese groups, who have found long term survival after alcohol injection to be comparable to surgical resection series (Livraghi et al, 1992; Shiina et al, 1993). Although large numbers of patients have been reported as being treated by alcohol, there has not yet been a randomised controlled study. Experience of treating liver metastases with alcohol injection is more limited and less effective (Masters et al, 1991; Amin et al, 1993). It may sometimes be effective at destroying small (<2cm) liver metastases, particularly from endocrine primaries, but is less likely to be effective in treating colorectal liver metastases (Livraghi et al, 1991). The reason for this is that colorectal liver metastases tend to be hard tumours, without a capsule, surrounded by soft liver, and so the tendency for injected alcohol is to track back around the needle into surrounding liver rather than stay in the tumour, through which it diffuses in an irregular and inhomogeneous way; in contrast, hepatocellular carcinomas are soft tumours with a fibrous capsule, often surrounded by hard cirrhotic liver, so that injected alcohol tends to remain within the tumour and diffuses through it relatively homogeneously (Amin et al, 1992).
Alcohol tracking back up and around the needle often spills into the peritoneal cavity causing severe pain, which is the main complication. Other side-effects of percutaneous alcohol injection are minimal.

Despite the advantages of being a cheap and simple technique, percutaneous alcohol injection is relatively ineffective for treating colorectal liver metastases; this was the unanimous conclusion of the First International Workshop on Liver Tumour Ablation (Chicago, Illinois, November 1992).

**1.3.4.4. Radiofrequency (RF) Electrocautery**

This is a promising, recently introduced technique in which a standard electrosurgical generator is used to apply radiofrequency energy interstitially, via a percutaneously introduced fine needle sheathed in non-conductive plastic (McGahan et al., 1990). The bare 1cm tip of the needle is placed into the desired target (i.e. tumour) using ultrasound guidance; the diameter of needle is about 1mm (18 gauge). During RF electrocautery a high frequency alternating current flows from the uninsulated tip of the electrode into surrounding tissue, and thermal damage occurs by ionic agitation - this results in frictional heating in the tissue around the electrode, rather than the electrode itself being a primary heat source (McGahan et al., 1990). Eventual drying of the tissue around the needle-tip causes a decrease in the current flow, and halting of thermal destruction (McGahan et al., 1990). *In vivo* experimental work in pig liver has resulted in the safe production of well-defined and predictable lesions of coagulative necrosis of 1-2cm in diameter, when using a coagulation setting on the electrosurgical unit for 1-2 minutes (Rossi et al., 1990; Sanchez et al., 1991; McGahan et al., 1992); the temperature at the needle-tip has been recorded as 90°C (Rossi et al., 1991). The extent of thermal damage is seen on ultrasound as an expanding echogenic zone around the needle-tip, and the size of the necrotic lesion is dependent on the type and dimensions of the probe as well as the energy settings used (Sanchez et al., 1991).

Clinical application of this technique has been reported by Buscarini et al. (1991) in 10 patients with small (1.2-3cm) but inoperable hepatocellular carcinomas; they claimed an immediate tumour destruction rate of 100% (all post-treatment biopsies were negative for tumour). Three patients remained free of tumour at 1 year follow-up, but recurrence was found in the other 7 patients.

RF electrocautery has the potential to be a safe, cheap and effective percutaneous technique for destroying small liver tumours, particularly if multiple electrodes are used. No patients with liver metastases treated by RF electrocautery have so far been reported.
13.4.5. Interstitial radiotherapy

The rationale for interstitial radiotherapy is that much higher radiation doses can be delivered to the tumour directly, sparing normal liver and so minimising hepatic toxicity, which is a common problem with external radiotherapy (Masters et al, 1991). Nauta et al (1987) treated 12 patients with inoperable liver metastases by inserting an iridium-192 source into superficial lesions at laparotomy; the length of the procedure varied from 3 to 7.5 hours, and out of 10 patients who had an initially raised CEA level, 6 showed a fall within 2.5 months of treatment. Dritschilo et al (1986) applied this technique percutaneously (under ultrasound guidance) using a 14 gauge needle applicator and a high intensity iridium-192 source. They treated 6 patients with colorectal liver metastases (size 2-9.5cm), and at 1 month follow-up there was a 25% tumour regression in 1 patient and no increase in tumour size in the other 5 patients. All that can be concluded from this study is that the technique is feasible, with little toxicity; the duration of patient response and survival were not mentioned.

Although interstitial radiotherapy has sound rationale for its use, the effects of treatment cannot be monitored during therapy, and further evaluation of its efficacy is required before its potential role can be determined.

13.4.6. Hyperthermia

Conventionally, hyperthermia indicates elevation of tissue temperatures to 41-45°C, this form of treatment often being practised by Radiotherapists/Oncologists mainly for superficial malignancies (Diamond et al, 1988); the rationale is that the tumour microenvironment (ie. low pH, low oxygen, and low glucose) makes tumour cells more heat sensitive than cells in normal tissue (Song et al, 1980). Combination of hyperthermic treatments with chemotherapy and particularly radiotherapy have been widely reported to give better tumour response compared to chemotherapy or radiotherapy alone (Perez et al, 1983; Green et al, 1989). Most centres use external applicators (microwave, radiofrequency, or low intensity ultrasound) to achieve moderate temperatures (41-45°C) in superficial tumours - this requires long exposure times (1-2 hours) for cell death to occur; cells die during their remaining cycle, which can take up to 1 week (Nishimura et al, 1989). These relatively small temperature rises inevitably result in non-uniform heating, with subsequent patchy and imprecise tumour destruction (Bleehen, 1982).

Targeting of deep-seated tumours has become possible with the use of interstitial heating devices (Emami et al, 1991), but the temperatures are still being kept below 45°C (Coughlin, 1990) - this is due to the desire to keep damage to normal tissues minimal, and also because of the concern that patients may not tolerate local elevations of temperature greater than 45°C. In organs such as the liver which often have small tumours surrounded by plenty of well perfused normal tissue, it is particularly difficult to keep temperatures around an interstitial heating device uniformly below 45°C. Furthermore, it is desirable to destroy a margin of surrounding normal liver as well as the tumour itself; therefore,
maintaining temperatures below 45°C is unlikely to be of any significant benefit when treating liver tumours.

Reports of true hyperthermia treatment to liver tumours are few. Nagata et al (1990) reported on 26 patients with liver tumours (20 with metastases and 6 with cholangiocarcinoma) who were treated with radiofrequency thermotherapy (temperatures kept below 44°C) combined with chemotherapy or radiotherapy; local response rates were 11% and 33%, respectively, which increased to 86% when embolization was also performed. The 1 year survival of these 26 patients was 50%. Storm et al (1982) also used radiofrequency hyperthermia to treat 10 patients with melanoma liver metastases, in combination with chemotherapy; tumour regression was found in 3 patients, there was no change in tumour size in 5 patients, and 2 patients had tumour progression. All patients died of progressive disease elsewhere.

Hyperthermia treatment to liver tumours has no proven survival benefit. It may have a potential role in the palliation of symptomatic patients, and for additive or synergistic effects when combined with chemotherapy or radiotherapy; the toxicity of the latter two modalities may then be reduced (Hugander, 1990).

Confusion with the terminology of heat treatments is frequently encountered. Although hyperthermia means elevated temperature, it has conventionally become defined as a uniform temperature rise to 41-45°C. Heating modalities using temperatures much greater than 45°C should preferably not be termed hyperthermic treatments, in order to avoid any confusion.

1.3.4.7. Conclusions of local treatments
There are a variety of local therapies available for liver tumour destruction. All show some degree of effectiveness. However, most of these treatments are still being evaluated, and as there are no controlled trials, it is not possible to make any valid comments on survival benefit. There are also no comparative clinical studies on the relative merits of the different modalities. The ideal local treatment should be simple to perform, cheap, readily available, minimally invasive, easily repeated, with minimal morbidity and no long term adverse effects. This latter point is especially important since the majority of patients who are suitable for local therapy have asymptomatic, small volume liver tumour. The objective of local therapy should be complete destruction of targeted liver tumour, except in the case of endocrine metastases, when debulking may be reasonable. Ideally, the tumour destruction should be amenable to monitoring with non-invasive modalities (such as ultrasound, CT or MRI). Patients who may be suitable for local therapy should have less than 10% replacement of liver volume by tumour, and preferably less than 5%; in addition, there should only be a small number of tumour deposits, since multiple small metastases are unlikely to be amenable to local therapy, even if the PHR is less than 5%.
The potential advantages of local therapy include low morbidity and mortality rates, short hospital stay, repeatability, and relatively safe treatment of lesions in close proximity to major vessels.

With further developments and improvements, local techniques may rival and improve upon the results of surgery, with much lower morbidity and negligible mortality rates for suitably chosen patients (Masters et al, 1991), particularly for tumours under 3cm in diameter.

Another promising local treatment of liver tumours is interstitial laser photocoagulation (ILP); this is a percutaneous technique in which tumours are destroyed by direct heating using low power laser energy. ILP is described in detail in chapter 2, and forms the subject of this thesis.

1.4. CONCLUSION OF TREATMENT OF LIVER TUMOURS

Considerable progress over the last few years has improved the techniques and available treatment options for managing patients with liver metastases. The only hope of cure is surgical resection, but this is effective in only a very small number of patients. Improved tumour detection and surgical techniques may mean that patients can be better selected for surgery with subsequent improvement in survival rates, and a consequent reduction in unnecessary operations. The majority of patients remain incurable and effective systemic treatment is urgently needed. Newer chemotherapy regimes show some promise, but further evaluation and considerable improvements are still needed. Regional chemotherapy improves local response rates but produces no convincing improvement in survival. Some new local treatments show promise, and with improved techniques may be capable of consistently destroying small (<3cm) liver tumours. On their own, local therapies are unlikely to improve survival. Using an effective local therapy with a more effective systemic therapy than is currently available could become a promising combination in the future; this would be of potential benefit to a large number of patients with liver metastases.

The treatment of patients with liver metastases should, whenever possible, be in the context of a carefully planned clinical trial, so that reliable information about the effects of treatment can be obtained. Once new treatment modalities have been shown to be capable of effectively and safely eradicating liver metastases, the aim should be to perform controlled, randomised trials. Since a no-treatment arm in such trials is unlikely to be acceptable to patients, comparative studies between different modalities should be performed. Unfortunately, only about 1% of patients with metastatic cancer enter prospective randomised trials (Kemeny et al, 1993). Currently, most asymptomatic
patients with liver metastases are not given any treatment, and are simply monitored until symptoms occur (Kemeny et al, 1993).
CHAPTER 2: INTERSTITIAL LASER PHOTOCOAGULATION (ILP)

Introduction

2.1. Principles of ILP

2.2. Laser-tissue interaction

2.3. Experimental work on ILP
   2.3.1. Terminology: ILP or ILH?
   2.3.2. Normal liver
   2.3.3. Tumour models
   2.3.4. Imaging of ILP

2.4. Clinical work on ILP

2.5. Conclusion
INTRODUCTION

Chapter 1 reviewed the different local methods for destroying liver tumours. Another local technique for tumour destruction, called interstitial laser photocoagulation (ILP), will be discussed in detail in this chapter.

The rationale for using local therapy for treating liver tumours has been discussed earlier. If surgical resection improves survival in selected patients, then complete in situ destruction of tumour as well as a margin of normal liver, could theoretically also improve survival in similarly selected patients. An effective, minimally invasive, local therapy may also be of potential benefit to a large number of patients who have small volume liver tumour but are unsuitable for surgery.

ILP is a percutaneous technique of tumour destruction in which tumours are slowly heated to temperatures exceeding the threshold for protein denaturation, using low power laser energy delivered directly to the tumour via thin flexible optical fibres.

ILP has undergone evaluation for the last 10 years and the majority of the work has been experimental. In common with many other new treatments for liver tumour destruction, ILP has not yet reached the stage of controlled clinical trials, but continues to evolve and improve as a technique of local tumour destruction.

In this chapter the principles of ILP and laser-tissue interaction will first be briefly discussed. A review of the relevant experimental and clinical literature on ILP will follow.

2.1. PRINCIPLES OF ILP

The principles of ILP were first described by Bown (1983). Thin (0.2-0.8mm) flexible optical fibres are inserted percutaneously, via hollow metal needles, so that the fibre-tip lies within the tumour to be treated. The other end of the fibre is connected to a laser which emits light of an appropriate wavelength. The laser is then activated at low power (1-3W) for a long exposure time (300-1000s). The laser light emitted from the fibre-tip penetrates and scatters in the surrounding tumour tissue, and is absorbed as heat, with subsequent denaturation and coagulation of the tissue proteins. This results in a fairly predictable, well-defined, spherical zone of coagulative necrosis around the fibre-tip. Maximum effect occurs at the desired site with minimal effects on other adjacent tissue, apart from the thin track required for insertion of the needle and optical fibre. The resulting in situ tumour necrosis is gradually resorbed, and healing occurs over several months, the necrosed tissue eventually being replaced by a small fibrous scar.
When the optical fibre-tip is buried in tissue, the response occurs in a very confined space. If the energy delivered is too fast, the result can be drastic. An excessive amount of tissue water may be vaporised, and since there is nowhere for this to escape, local pressure disruption of tissues may occur; also, the fibre-tip can be damaged if it gets too hot while in contact with biological material. Thus, interstitial therapy is best carried out at relatively low laser powers (less than 5W).

For ILP to be safe, it is essential to be able to predict the nature, extent and healing of the tissue damage that given laser parameters will produce; this is particularly important since it is not possible to assess the results of ILP by any immediate visual effect. Hence, the laser parameters need to be carefully evaluated and defined by in vivo experimental work, so that a predictable size of necrosis can be produced by appropriately selected parameters. Ideally, an accurate, non-invasive monitoring modality is also desirable, since biological variability can reduce the predictability of tissue response to ILP.

ILP is most suitable for tumours of solid organs, which are surrounded by plenty of normal tissue. Small tumours in the liver are particularly suitable for ILP, since the liver is a well-perfused organ (which assists in containing thermal damage around the fibre-tip) and has excellent regenerative potential (allowing destruction of significant volumes of tissue).

2.2. LASER-TISSUE INTERACTION

A laser is a device which amplifies light to produce an intense beam, and differs from other light sources in that it produces a beam which is coherent, monochromatic and highly collimated (Carruth and McKenzie, 1986). These properties allow laser light of appropriate wavelength to be delivered in a precise, controlled and predictable manner to a very small area. The laser light is transmitted by thin flexible optical fibres, and the effects produced are limited to the desired target area.

Lasers are playing an increasingly important role in a wide variety of clinical applications. They deliver light energy to tissue with great precision, and can produce a range of tissue effects. For the majority of clinical applications, the most important laser-tissue effects are thermal, and include tissue vaporisation, necrosis, and coagulation (Bown, 1991). Medical lasers are widely used in the non-contact mode, with the fibre-tip a few millimetres above the target area, which is vaporised using high powers (50-80W) over a short exposure time (1-2s); this technique is commonly used to recanalise advanced obstructing cancers of the oesophagus or bronchus (Fleischer, 1984; Hetzel et al, 1985). In contrast, ILP is performed with relatively low powers (less than 5W) over a long exposure time (300-1000s), with the fibre-tip buried within the tissue - this gives rise to
slow and controlled heating, and a gradually enlarging zone of coagulative necrosis around
the fibre-tip (Bown, 1983).

There are several types of lasers, each producing light of a specific wavelength in the
electromagnetic spectrum. The three main medical lasers which have been used for their
thermal effects are: the carbon dioxide (CO\textsubscript{2}) laser with a wavelength of 10600nm in the
far infra-red part of the spectrum; the neodymium ytrrium aluminium garnet (Nd:YAG)
laser with a wavelength of 1064nm in the near infra-red part of the spectrum; the Argon
ion laser which has two main lines at 488nm and 514nm in the blue and green region,
respectively, of the visible spectrum. There are two new lasers which are currently
undergoing evaluation of their potential utility in clinical practise. These are the Nd:YAG
laser producing a wavelength of 1320nm (Mordon et al, 1990; George et al, 1991), and a
portable diode laser (gallium aluminium arsenide, GaAlAs) with a wavelength of 805nm
(Manni, 1992; Wyman et al, 1992).

The light which is emitted from the fibre-tip during ILP may be reflected, transmitted,
scattered or absorbed, the latter resulting in heat deposition in the tissue with subsequent
thermal damage (Fisher, 1992). The tissue changes which take place are related to the
temperature reached and the time for which the tissue remains at these temperatures
(Thomsen, 1991). At temperatures below 45°C tissue effects are only produced over a
long time (30 minutes to several hours) and are often reversible. They include mitotic
arrest (Sisken et al, 1965), decreased cell metabolism (Muckle and Dixon, 1971), fall in
cellular oxygen and pH (Bicher et al, 1980), and changes in local blood flow (Dudar and
Jain, 1984). At 45-99°C there is irreversible denaturation of tissue proteins and
coaugulation occurs. The changes that take place are similar to those seen during heating of
egg-white, and their production is dependent on the length of time for which a temperature
is maintained, this being shorter at higher temperatures (Priebe et al, 1975). At
temperatures greater than 100°C tissue water boils; the conversion of water to steam
results in a thousand-fold expansion and the cell walls rupture, allowing steam to escape
(Carruth and McKenzie, 1986; Brackett et al, 1986). During ILP, with the heating
occurring in a closed space, the steam escapes along tissue planes and into any adjacent
blood vessels. Once the water around the fibre-tip has dried, the temperature will rapidly
rise to 300-400°C, with subsequent tissue blackening, carbonisation and smoke

The extent of thermal necrosis occurring in tissues is dependent on the laser wavelength
used, energy deposited, and the thermal and optical properties of the target tissue
(Svaasand et al, 1985). The absorption of laser light in tissue is highly dependent on its
wavelength (Blanc and Colles, 1990). It is the absorbed energy which produces the
biological effect, but reflection, transmission and scattering determine where the light
goes, and consequently the volume of tissue in which it is absorbed. During ILP, the laser
beam exits from the fibre-tip and undergoes multiple scatterings in the surrounding tissue, so that the light becomes distributed in an almost spherical pattern around the fibre-tip (Matthewson, 1991). The size of this spherical distribution depends on the optical penetration of the light into the tissue, which in turn depends on the wavelength of the light and the optical properties of the tissue (Blanc and Colles, 1990; Svaasand et al, 1985). The 1064nm Nd:YAG laser has excellent tissue penetrating qualities and is highly scattered compared to the other medical lasers (Bown, 1983); it can penetrate pure water up to 90mm (Haldorsson and Langerholc, 1978), but in soft tissue this decreases to a few millimetres (Haldorsson et al, 1981; Brackett et al, 1986) due to increased absorption by blood (Jacques et al, 1992) and increased scattering by tissue inhomogeneities (Svaasand et al, 1985). In contrast, the CO\textsubscript{2} laser beam is highly absorbed in water and penetrates to a depth of only 0.1mm in soft tissue, with minimal scattering; it is used mainly for cutting in surgery (McKenzie and Carruth, 1984). The Argon laser light is also more heavily absorbed than the 1064nm Nd:YAG laser light, with a soft tissue penetration of around 1mm, absorption occurring mainly in haemoglobin and melanin; this laser is used in ophthalmology and for treating port wine haemangiomas (Dolsky, 1984).

The two new laser wavelengths (1320nm and 805nm) are currently being evaluated for possible clinical roles. Compared to the 1064nm Nd:YAG laser, the 1320nm Nd:YAG wavelength is more heavily absorbed in water, less absorbed in blood and less scattered in blood-containing tissue (Frank et al, 1987). In vivo work on canine gastric mucosa has shown that the 1320nm wavelength produces similar volumes of vaporisation as the 1064nm, but 3-4 fold greater volumes of coagulation (Heldwein et al, 1987). The depth of soft tissue penetration of the 1320nm Nd:YAG laser has been shown to lie between that of the CO\textsubscript{2} laser and the 1064nm Nd:YAG laser (Mordon et al, 1990). The 805nm diode laser has a similar scattering coefficient to the 1064nm wavelength in liver, but an absorption coefficient 3.5 times greater (Jacques et al, 1992). The increased absorption of the 805nm wavelength occurs principally in deoxygenated blood, in which it is 15 times more strongly absorbed than the 1064nm wavelength (Cheong et al, 1990). During non-contact laser therapy, the 805nm wavelength is more strongly absorbed and has less penetration depth than 1064nm, and may be more effective for cutting tissue (Jacques et al, 1992). Experimental work has shown that, overall, there are more similarities than differences with respect to the soft tissue laser-tissue interaction (Jacques et al, 1992; Wyman et al, 1992).

Hence, from the above discussion, it is clear that the 1064nm Nd:YAG laser gives the deepest penetration of laser light into soft tissue, and so theoretically should give rise to the largest volumes of thermal necrosis (Svaasand, 1989). This theoretical assumption combined with the fact that Nd:YAG laser light is easily transmitted down thin flexible fibres, has made this laser widely accepted as the most suitable laser for ILP. This has resulted in virtually all of the current work on ILP being performed using the 1064nm
Nd:YAG laser, with no comparative studies to evaluate the actual effects of less penetrating wavelengths during ILP. The experimental section (chapter 4) of this thesis addresses this question, and shows that the theoretical assumptions are, in practise, wrong, when it comes to finding the best way to apply ILP.

2.3 EXPERIMENTAL WORK ON ILP

2.3.1. TERMINOLOGY: ILP or ILH?

2.3.2. ILP TO NORMAL LIVER

2.3.3. ILP TO TUMOUR MODELS

2.3.4. IMAGING OF ILP

Most of the experimental work on ILP has been concerned with the determination of appropriate technical parameters (optimal fibre-tips, power and exposure time) and assessing its safety and efficacy using animal models. Most studies have used normal tissue, with more limited data available on tumour models. The appreciation of the importance of imaging in ILP has prompted several studies to evaluate the role of ultrasound and magnetic resonance imaging during and after ILP. Although the experimental studies have used several different tissues in vitro and in vivo, including pancreas (Nuutinen et al, 1992), brain (Schatz et al, 1992) and prostate (McNicholas et al, 1993), most of the literature is on liver tissue, and these studies will form the main subject of this review section.

All of the work on ILP has to date been performed using the Nd:YAG laser with a wavelength of 1064nm.

2.3.1. TERMINOLOGY: ILP OR ILH?

There is some confusion with the terminology used to describe interstitial laser therapy. Several groups call this technique interstitial laser hyperthermia (ILH), although some are now preferring the term interstitial laser photocoagulation (ILP). The problem with using the term "hyperthermia" is that this conventionally indicates fairly uniform temperature rises to 41-45°C for up to several hours, so that cells die during the remaining cell cycle over several days (see section 1.3.4.6). However, using laser powers of 1.5-3W over 5-15 minutes with bare optical fibres results in immediate tissue necrosis around the optical fibre-tip (Thomsen, 1991), and much higher tissue temperatures than those used during hyperthermia. Therefore, this form of treatment should preferably not be called hyperthermia (Sweetland et al, 1989), and a more accurate term is photocoagulation. Unfortunately, this has not yet become generally accepted, and many authors are still using the term hyperthermia inappropriately. To add to the confusion, some groups are...
trying to avoid very high temperatures (and tissue charring) by using a diffusing optical fibre-tip and intentionally keeping the temperatures below 45°C with a computer-linked feedback system (Daikuzono et al., 1987; Panjehpour et al., 1990); this can be described as hyperthermia, but does not use the potential of lasers to cause immediate tissue necrosis, and appears to offer no real benefit over non-laser hyperthermic treatments.

2.3.2. ILP TO NORMAL LIVER

ILP has been performed in normal rat, rabbit and pig liver, in vivo. Many studies have used low power (0.5-4W) over a long exposure time (50-2400s) and a bare optical fibre-tip. There has also been much interest in various modified fibre-tips, often with much higher laser powers, and multiple fibres have also been used. The predominant pathological finding is that of a well-defined, fairly uniform zone of coagulative necrosis around the fibre-tip, with relative sparing around larger blood vessels because of the cooling effect of flowing blood; with the bare fibre-tips and/or at higher powers, a small central cavity surrounded by a thin zone of charred tissue (due to the high temperatures around the fibre-tip) is also present.

2.3.2.1. Bare fibre-tip work

This is the simplest way of performing ILP; the optical fibre tip is plane-cleaved at its distal end, and sometimes the distal 3-5mm of cladding and/or jacket is also stripped, leaving the exposed core or cladding at the fibre-tip. The earliest and most comprehensive work was performed by Matthewson et al. (1987) in rat liver, using a 0.4mm optical fibre. They originally used a pulsed laser (0.1ms pulses at 40Hz) but subsequently showed that the results were identical to those obtained with a continuous wave laser (Matthewson et al., 1986). Well-defined, symmetrical and reproducible necrotic lesions up to 16mm in diameter were found, which increased in size with increasing power and energy, although there was a plateau effect above a power of 1W and energy of 600J. Above 0.75W charring around the fibre-tip was almost universal, but was reported as being disadvantageous. Temperatures of up to 100°C were recorded at the fibre-tip, dropping to 52°C 8mm away, using a power of 2W. The relative light intensity 4mm away from the fibre-tip fell to 27% of its initial value after a 200s exposure at 2W, indicating that the optical properties of liver can change markedly during ILP. Arteriography demonstrated loss of all small and some large (up to 1.5mm diameter) vessels in the treated area. All lesions healed by regeneration, without complication, within 60 days, leaving a small fibrous scar.

Matsumoto et al. (1992) performed ILP in rabbit liver using a 0.6mm plastic clad fibre. At powers of 2W and energy of 600J, the longitudinal (along the fibre-track) and transverse (perpendicular to the fibre-track) diameters of necrosis were 17mm and 13mm, respectively; at 3W and 900J, these diameters increased to 27mm and 15mm,
respectively. The variation in the longitudinal diameters at 3W was significant, with a standard deviation of +/-5mm. This can be explained by the fact that at 3W there is greater heating in front of the fibre-tip and a small cavity forms. This cavitation causes a forward shift of the point of energy absorption, which in turn results in a more ellipsoidal lesion, with a more variable length.

Dachman et al (1990) performed ILP in pig liver using a 0.6mm optical fibre, and powers of 1-4W for 300s in order to produce necrotic lesions measuring about 1cm in diameter. They showed that the necrosis heals safely over 7 weeks, the only abnormality being a mild and transient rise in serum liver function tests. The same group reported a further study in pig liver correlating temperature rises with necrotic lesion morphology (Dachman et al, 1991). Powers of 0.15-3.8W were used for 360s, and the subsequent size of necrosis was roughly proportional to the cube root of the power. Powers of 0.5-1.6W produced lesions of 9-19mm in diameter (mean 8.5mm), with a maximum temperature of 244°C at the fibre-tip and 56°C 4mm away. Powers of 1.7-3.9W produced 10-20mm lesions, and temperatures of 597°C at the fibre-tip and 102°C 4mm away. No mention was made whether the thermocouples were gold plated so that they would not directly absorb laser light. Bosman et al (1991) also used a 0.6mm fibre to produce three ILP lesions in the liver of each of four pigs, with a power of 1.5W for 600s. The variation in necrotic lesion size was marked: immediate evaluation showed sizes of 3mm, 10mm, and 11mm; in another pig, one week later the sizes were 0mm, 10mm and 12mm; in the third pig, at 2 weeks the sizes were 0mm, 5mm and 5mm; in the fourth pig, no lesion could be identified at 4 weeks. The authors explained this variation by the fact that some of the smaller lesions were adjacent to blood vessels; they also stated that the larger part of the necrosis developed during the first week, although their data is insufficient to support such a claim.

Higuchi et al (1992) used slightly higher powers for ILP to rat liver. At 9W and energies of 45-360J ellipsoid necrotic lesions were produced, the transverse diameter plateauing at 5mm with energies of 180J or above; the longitudinal diameter continued to increase with increasing energies, being 12mm at 200J and 16mm at 360J. They also used a constant energy of 180J, and increased the power from 2W to 18W; at 2W fairly circular necrotic lesions were produced measuring 5mm in diameter, but at 4W or above the longitudinal length of necrosis increased, plateauing at 12mm above 9W. Cavitation around the fibre-tip was seen at 4W or above, which is the reason for the ellipsoid lesions (see above). Plateauing of the transverse diameters is expected since the focus of energy is propagating forwards; this was also observed in the longitudinal diameters with powers above 9W, presumably because of the relatively short exposure times.

These studies on bare fibre-tip ILP have shown that low power (less than 3W) application can consistently produce fairly symmetrical necrotic lesions of 10-20mm in diameter, the
sizes in the larger pig livers being slightly smaller than in rabbit or rat liver, which is likely to be due to the greater loss of heat in the former to the large volume of surrounding vascular tissue. The size of necrosis produced by a bare fibre-tip is limited by the power which can be safely applied, to avoid forward channelling of the light beam.

2.3.2.2. Multiple fibre-tip work
In order to safely increase the volume of tissue necrosis, and still use one laser as the energy source, beam splitters or fibre-optic coupling systems have been used (Steger and Bown, 1989; Joffe et al, 1989). These allow simultaneous activation of several optical fibres. The most promising system tested has been the 1x4 Star Coupler (Canstar, Canada), which is made by the fused biconic technique. This allows equal splitting ratios from a single input optical fibre to 4 output fibres, and the power outputs remain stable despite the loss of up to 40% of the input power at the fibre junctions (Steger, 1991). This coupler has been used to produce thermal necrosis in normal canine liver (Steger et al, 1992). The optimal parameters for producing uniform necrosis were found to be a power output of 1.5W per fibre, an exposure time of 670s, and fibre-tip spacing of 1.5cm positioned approximately at the 4 corners of an arbitrary square. This set-up gave well-defined, spherical necrotic lesions of up to 4cm in diameter. Tissue charring was consistently seen at the sites of the fibre-tips, and the recorded temperature in the centre of the necrotic lesion (10mm from the fibre-tips) was 60°C after 500s of ILP. There was one complication of an hepatic abscess one month after ILP, and there were transient rises in serum liver enzymes by 24hrs which returned to normal by 60 days. Liver angiography showed a clear "hole" in the treated area with no arterial supply to the laser-induced thermal necrosis. Healing occurred safely and by 1 year, only 4 small chars remained in normal liver.

One of the problems with beam splitters is excessive heating of the coupler when using powers above 1.5W per output fibre, which may result in permanent damage. Another difficulty is in good alignment of the beam from the laser with the input fibre of the coupler; this requires very careful construction of an appropriate connector, otherwise the connector rapidly "burns out". These are the main reasons why beam splitters have not so far been more widely used.

2.3.2.3. Modified fibre-tip work
Several groups have developed various diffuser fibre-tips to increase the surface area from which tissue heating occurs. The first of these was the artificial sapphire probe which was made of a ceramic material with a high melting point and great tensile strength (Daikuzono and Joffe, 1985). Most proponents of these sapphire tips combine their use with thermocouple-linked feedback systems to keep temperatures below 45°C, the objective being to increase light diffusion into tissue (Joffe et al, 1989). Tissue charring is avoided by using flowing saline, although initially gas cooling was used resulting in fatal air
embolus (Baggish and Daniell, 1989; Schroder et al, 1989). Several studies have shown that sapphire tips are less effective at producing necrosis and are less efficient than bare fibre-tips (Castren-Persons et al, 1992; Karanov et al, 1992), with up to half of the delivered energy lost in coupling to the sapphire tip (van Eeden et al, 1988); these tips are also too large for percutaneous use. Malone et al (1992) performed a comparative study between plane-cut bare fibre-tips, and specially designed cylindrical diffusing fibre-tips and spherical diffusing fibre-tips, in pig liver. They found that the bare fibre-tips produced much more effective necrosis than the diffusing tips, the latter being unable to withstand powers of 3-6W. Van Eeden et al (1988) also evaluated fibre-tips following chemical stripping of the cladding or silica etching by hydrofluoric acid, but found no advantage of these modifications over bare fibre-tips. Huang et al (1991) surrounded a bare fibre by a light diffusing material to produce a 10x1.8mm fibre-tip; interstitial application to rabbit liver at 2-3W for 10 minutes resulted in a 1cm diameter necrotic lesion, although temperatures over 42°C were achieved in a 3cm diameter zone around the probe. Higher powers were not used for fear of damaging the probe. More recently, Nolsoe et al (1992) have described a diffuser tip made by grinding the distal 2-3mm of the quartz core of a bare optical fibre, to give a cone shaped frosted diffuser tip, with a maximum external diameter similar to the unmodified bare fibre-tip (0.6-0.8mm). This emits light in a roughly spherical distribution. In vitro evaluation in pig liver with a power output of 4W for 600s resulted in spherical necrotic lesions (mean diameter 23.5mm) with the diffuser tip compared to cylindrical lesions (mean length 40mm, mean diameter 15mm) with the bare fibre tip. The diffuser tip produced necrotic lesions up to 44mm in diameter with central cavitation and charring, using a power of 4W for 1800s (energy 7200J); the size of cavitation remained constant at 10mm at energies above 2400J, while the zone of coagulation continued to increase as the energy increased.

Most of these studies have shown that most modified fibre-tips are no better than bare tips for ILP. The recent report from Nolsoe et al (1992) shows that their thin diffuser tips can tolerate higher powers and allow larger necrotic lesions to be safely produced at these powers, which is not possible with bare fibres (see section 2.3.2.1).

2.3.2.4. High power work
Lasers have been applied at high powers to the liver surface. This leads to areas of necrosis which heal, but when applied to implanted tumours can cause dissemination as a result of the ferocity of tissue disruption from a pulsed laser (Hoye et al, 1968). More recently, Godlewski et al (1988) have used a purpose-built hand-piece to deliver 80-100W interstitially to pig liver, at laparotomy. The fibre-tip was cooled with circulating saline. Using 80W for 10s resulted in 12-18mm lesions consisting largely of vaporised tissue; the temperature at the fibre-tip was 440°C, falling to 86°C 10mm away, and 53°C 15mm away. Ultrasound showed an echogenic spherical lesion which correlated with the pathological size of necrosis; sometimes the lesion had irregular margins on ultrasound.
with lateral extensions into the perivascular spaces. No complications were apparent, and healing occurred safely over 4 months. However, if this technique is used to treat tumours, the rapid build-up of energy is likely to result in pressure disruption and dispersion of some tumour cells into the systemic circulation. The short heating time (10s) means that some of these cells will remain viable. The short treatment time also precludes adequate monitoring and control of the thermal effects of treatment. The large diameter of the hand-piece (5mm) precludes percutaneous application.

2.3.2.5. Histological features of ILP
Several groups have reported in detail the histological features of ILP-induced necrosis, and there is fairly general agreement on the findings. A central zone of cavitation and charring is surrounded by a broad zone of coagulative necrosis, which is bounded by a transition zone of inflammatory cells, outside which is normal liver (Matthewson et al, 1987; Dachman et al, 1990; Bosman et al, 1991; Matsumoto et al, 1992). The central cavitation and charring are due to the very high temperatures around the fibre-tip, tissue water boiling, and steam formation (Brackett et al, 1986; Thomsen, 1991). The zone of coagulative necrosis comprises the bulk of the lesion and is more apparent 24hrs after ILP (Matthewson et al, 1987; Steger et al, 1992). By 4-7 days, granulation tissue is seen in the periphery of the lesion, with infiltration of neutrophils, giant cells and macrophages, and the appearance of proliferating bile ductules and neovascularisation (Matthewson et al, 1987; Bosman et al, 1991). This is followed by a gradually enlarging fibrous capsule, and the necrotic tissue is replaced by phagocytosis and liver regeneration, eventually only a small fibrous nodule remaining (Matthewson et al, 1987).

2.3.3. ILP TO TUMOUR MODELS
Karanov et al (1992) performed ILP with a bare fibre on transplanted flank tumours (mammary adenocarcinoma) in mice using 1W and 1200J, and 3 days later found necrosis of up to 60% of tumour volume (mean diameter of necrosis was 5.4mm). Matthewson et al (1989) performed bare fibre ILP on rat transplanted fibrosarcoma (tumour size 1.5cm), and completely destroyed them in 10 rats using 2W and 1200J; follow-up showed no evidence of recurrence in 5 of these rats, and survival was significantly improved compared to an untreated group (median survival was 70 days and 30 days, respectively). Dowlatshahi et al (1992) used higher powers of 5W but with saline flow to keep the bare fibre-tips cool and prevent charring, and kept temperatures 1mm from the fibre-tip below 45°C. They found a linear relationship between the energy deposited and volume of necrosis following ILP to a rat mammary carcinoma; 1500J of energy resulted in a mean volume of necrosis of 2.4cm³. ILP to a VX2 tumour in rabbit liver with 3-4W for 20 minutes was found to be effective for destroying tumours less than 500mm³ in volume (Bito et al, 1993). Dachman et al (1992) also performed ILP to a VX2 carcinoma in rabbit liver; they applied 1-2W for 360s, and found smaller necrotic lesions (less than 1cm) and
lower temperatures (50-100°C, 2mm from fibre-tip) in the tumour compared with ILP to normal liver (Dachman et al, 1991).

These results show that tumours can respond differently to ILP. This is partly due to different techniques used to perform ILP, but is also likely to be due to the variable optical and thermal properties of different tumours. This also emphasises that applying ILP to human tumours may well require different laser parameters to those optimised on normal animal liver. Ideally an accurate monitoring modality is needed which can evaluate the effectiveness of ILP during and after treatment. This requires imaging which is discussed below.

2.3.4. IMAGING OF ILP

Although one of the main advantages of ILP over other treatment modalities is that it allows delivery of a precise energy dose to the target area, the effect on the tissue may be different at different treatment sites even if the same energy is used. This is due to the reasons discussed above as well as biological variability (Cheong et al, 1990), fibre-tip deterioration during ILP, and changing optical and thermal properties of the tissue during ILP (Svaasand et al, 1985). This means that accurate real-time monitoring of thermal effects during ILP and accurate assessment of the full extent of necrosis after ILP are very important for its success. Thermocouples give only single point temperature measurements, and are of relatively little value clinically because they are invasive and may absorb light and contribute to tissue heating (Philipp et al, 1993); in addition, intratumoral temperatures have a non-uniform distribution during heat treatment (Fessenden et al, 1984). Imaging provides a non-invasive way of monitoring the tissue changes during and after ILP. Experimentally, ultrasound (US) and magnetic resonance imaging (MRI) of ILP have been evaluated.

2.3.4.1. Ultrasound of ILP

Several in vivo studies in dog and pig liver have used ultrasound to monitor ILP. During ILP, a bright spherical and expanding echogenic zone is seen around the fibre-tip, which is due to tissue water boiling and microbubble formation (Thomsen, 1991). Dachman et al (1990) found the initially strong echogenic focus to decrease slightly and echogenicity 10 minutes after ILP. Bosman et al (1991) found the size of the echogenic lesion on ultrasound to plateau after 6-8 minutes of ILP, using a power of 1.5W, and decrease slightly in size 2 minutes after ILP. Steger et al (1992a) reported a delay of 20-30s before the sudden appearance of the brightly echogenic zone, which was also surrounded by a thin hypoechoic rim (approximately 3mm); the whole lesion expanded for 300-400s, using a power of 1.5W, then plateaued. During healing, the echogenic lesion decreases in size over several weeks and also develops a more echogenic rim due to inflammatory repair and fibrosis (Dachman et al, 1990; Bosman et al, 1991). Good correlation of the
size of the echogenic lesion on ultrasound with pathological size has been reported, at the end of ILP and at various times after ILP (Bosman et al, 1991; Nolsoe et al, 1991; Steger et al, 1992a). Malone et al (1992) emphasised that ultrasound images taken immediately after ILP tended to overestimate the size of necrosis, but later images (2hrs after ILP) better approximated the true extent of necrosis with a tendency to slightly underestimate the actual size. Steger et al (1992a) also monitored the tissue changes occurring in dog liver when activating 4 fibres simultaneously, placed 1.5cm apart. An expanding hyperechoic zone was seen around each fibre-tip, surrounded by a hypoechoic zone, the latter gradually coalescing by 670s, when using a power of 1.5W per fibre. The margins of the acute echogenic zone are sometimes poorly defined, with irregular echogenic streaks radiating away from it and trails of microbubbles seen "washing" away in nearby vessels (Bosman et al, 1991; Nolsoe et al, 1991; Steger et al, 1992).

Ultrasound is limited by the fact that it is essentially imaging microbubbles and charring, and is unlikely to depict thermal damage if temperatures are not high enough to cause microbubbles but are still adequate for cell death. Furthermore, the field of view may become distorted with echogenic streaks. Ultrasound is also operator dependent, and is unlikely to differentiate treated from untreated tumour, since the echogenic properties of coagulative necrosis are likely to be similar to those of tumours, and also because tumours are heterogeneous.

2.3.4.2. Magnetic resonance imaging (MRI) of ILP
MRI is less operator dependent and has better soft tissue contrast than ultrasound. MRI is also very sensitive to tissue water mobility and distribution (Bottomley et al, 1984), and there is a temperature dependence of MR relaxation parameters such as T1 relaxation time and diffusion coefficient (Dickinson et al, 1983; Le Bihan et al, 1989). Since the acute effects of laser irradiation cause a significant rise in tissue temperature (affecting the thermal motion of protons), and the distribution of water is altered in ILP-induced necrosis, MRI may theoretically have a significant role to play in ILP as a non-invasive monitoring modality. Furthermore, the multiplanar and 3-dimensional capability of MRI makes it particularly suited for evaluating the spatial distribution of thermal tissue damage (Knuttel and Juretschke, 1986). These factors have resulted in considerable interest being generated in the evaluation of MRI of laser-tissue interaction.

The earliest work on MRI of laser-induced tissue damage was by Jolesz et al (1988) who performed ILP in rabbit brain and mouse flank tumour. They found a large expanding zone of signal loss around the fibre-tip during ILP, on T1 weighted, T2 weighted, and proton density spin-echo sequences; the majority of this signal loss was reversible, with a small irreversible component immediately around the fibre-tip. A hysteresis was also found in the relationship between T1 and T2 weighted signal intensities and tissue temperature during and after ILP, indicating that MRI has a limited role as a tissue
thermometer. A reversible signal loss during ILP has also been found by others in vitro and in vivo, using T1 weighted standard spin-echo (Higuchi et al, 1992), fast spin-echo (Matsumoto et al, 1992), and gradient-echo (Marchesini et al, 1992) sequences, and is thought to be due to a temperature dependent change in the tissue T1 relaxation time (Parker et al, 1983). The maximum size of signal loss was found to roughly correspond to the extent of necrosis induced by ILP (Marchesini et al, 1992; Matsumoto et al, 1992), although its boundaries were not clearly demarcated because of the gradual rather than abrupt decline in temperature at the transition between necrotic and normal tissue. Marchesini et al (1992) measured the changes in T1 relaxation times of bovine liver during ILP using 2W, in vitro. They found an increase in T1 from 115ms before ILP to a maximum of 2500ms after 15 minutes of irradiation; the T1 relaxation time at the margin of the necrosis was approximately 350ms, during ILP. Muller et al (1992) proposed using sequence parameters which would give complete signal loss at a specified temperature (chosen as 45°C); they determined the T1 relaxation time at 45°C, and used this to calculate the inversion time (TI) required to produce zero signal intensity during a turbo-FLASH sequence. Application of these parameters to image ILP of rabbit liver showed a dark (no signal) band moving away from the fibre-tip during ILP, which represented an isothermal region at 45°C. Because of the temperature gradients achieved during ILP, it can be assumed that beyond this band the temperatures are below 45°C and within it they are above 45°C.

The rapid change of temperature during ILP means that real-time imaging is only of value if very rapid MR sequences are employed; diffusion sensitive echo-planar imaging (acquisition time 150ms) during ILP has successfully shown thermal change as signal loss in rabbit brain (Bleier et al, 1991). However, the long echo times required to produce diffusion weighted images mean that the signal intensity from liver is low due to its short T2. This would make it difficult to identify a further decrease in signal intensity related to the temperature rise during ILP. Respiratory motion of the liver could also cause considerable artefact during diffusion MRI, unless very rapid imaging is used (echo-planar imaging or turbo-FLASH).

Following ILP, T2 weighted sequences show the necrosis with the best contrast, and this appears as a low signal intensity zone surrounded by a high signal intensity rim (Anzai et al, 1992; Higuchi et al, 1992; Tracz et al, 1992). Anzai et al (1992) found the high signal intensity rim to correspond to oedema, which progressed to necrosis by 7 days after ILP. They also claimed that on serial images the necrosis reached a maximum size 7 days after ILP; however, they did not use any markers to define the imaging plane, which was clearly different on the days imaging was performed. Tracz et al (1992) used T2 weighted spin-echo sequences to image cat brain during and after ILP. They found the signal loss during ILP to underestimate the pathological size of necrosis found 2 days later. Images immediately after ILP also underestimated the necrosis at 2 days. T2 weighted images
taken just before killing the cat (at 2 days) slightly overestimated the extent of necrosis. However, they also used gadolinium enhanced T1 weighted sequences immediately after ILP, and found these to most precisely predict the extent of necrosis 48hrs later.

This summary represents the early evaluation of MRI of ILP induced thermal damage. The results are promising, but in vivo work applied to liver is still needed, to optimise MR sequences and more clearly define how accurately MRI can predict the true extent of thermal damage.

Ultrasound has some limitations as a real-time monitoring device, but does give an indication that thermal damage is taking place, and is likely to be useful clinically; problems may occur with accurately defining the margins of thermal damage. Ultrasound is also useful for monitoring healing, but there are likely to be problems in detecting recurrent tumour.

There has so far been no experimental animal work assessing the role of computed tomography (CT) to evaluate ILP-induced necrosis. Clinically, ultrasound and CT have been used during and after ILP, but no work on MRI has been performed on patients having ILP to their liver tumours.

2.4. CLINICAL WORK ON ILP

Initial clinical work with ILP was undertaken at laparotomy. Hashimoto et al (1985) used a modified diffuser fibre-tip inserted into the liver under ultrasound guidance to deliver up to 14000J at a power of 5W from a Nd:YAG laser. They treated 2 cases of hepatocellular carcinoma and 8 cases of liver metastases; an enlarging echogenic area was seen on ultrasound and treatment continued until this replaced the whole tumour. A moderate and transient rise in hepatic transaminases was noted, and significant falls in serum tumour markers were achieved. Hahl et al (1990) treated 7 patients with liver tumours (1 primary and 6 secondaries), again at laparotomy, using a sapphire fibre-tip at a power of 6W for 10 minutes. Fine-needle biopsies 3-5 days later showed evidence of necrosis in all treated tumours; however, in 30% of cases viable tumour cells were also seen in the necrotic tissue. CT follow-up at 4 weeks showed sharply bordered hypodense areas up to 2cm in diameter, which were assumed to represent necrosis. However, one patient died from an air embolus due to the use of coaxial gas to cool the sapphire fibre-tip (Schroder et al, 1989), and subsequent cooling was with flowing saline; another patient developed a subphrenic abscess.

Percutaneous, ultrasound guided ILP, was first reported by Steger et al (1989a); two patients with liver metastases were treated, in one patient by using 4 fibres fired
simultaneously (via a 1x4 coupler) to increase the extent of thermal damage. Necrotic changes within the tumour were seen on CT in one patient, and confirmed from core biopsies in the other patient. Dowlatshahi et al (1992a) treated one patient with a recurrent hepatoma (4.5cm), under general anaesthesia. They used a single bare fibre inserted percutaneously (5W, 21000J), with saline flow to keep the fibre-tip cool. Echogenic changes were seen on ultrasound during ILP, and 6 weeks later CT scan showed small low density necrotic areas within the tumour, which were confirmed on biopsy. The tumour growth was said to be halted for 3 months, after which there was progression and the patient died 9 months after ILP. Dachman et al (1992a) also reported one case who had 10 colorectal liver metastases, treated with a 1x4 coupler using 1W per fibre for 8 minutes. Similar ultrasound changes were seen, and contrast CT showed non-enhancing low density areas after treatment. Huang et al (1991) used a specially designed diffuser fibre-tip and a power setting of 2-3W for 20-30 minutes. They treated five patients with small hepatomas. Guided biopsies were taken from four patients following treatment, and all showed evidence of necrosis. In one patient there was no recurrence after 16 months of follow-up, three patients had recurrent disease after 5, 12 and 18 months, and one patient died of liver failure after 2.5 months which was thought to be unrelated to the laser therapy.

More recently, Masters et al (1992) and Nolsoe et al (1993) have reported larger series of percutaneous ILP. Masters et al (1992) treated 18 metastases in ten patients using a 1x4 coupler and 1.5-2W per fibre. Ultrasound showed thermal damage as increased echogenicity and enhanced CT showed necrosis as a new area of non-enhancement. Seven metastases (diameter 3cm or less) had necrosis of 30-100% of their volume at 2 months follow-up; larger metastases had minimal necrosis or no necrosis. All patients tolerated the procedure well. Nolsoe et al (1993) used a thin diffuser tip (power 4-8W for 5-45 minutes) to treat 11 patients with 16 colorectal liver metastases (size 1-4cm); ten of these patients had the procedure under general anaesthesia. The fibre-tip was placed in the centre of the tumour, and a thermocouple at its margin; the objective was to treat the tumour until the thermocouple recorded a temperature of 60°C, or a temperature of 45°C was maintained for at least 15 minutes. Ultrasound during treatment showed the typical hyperechoic zone, but afterwards a central cavity was apparent. This was confirmed pathologically in one tumour which was resected after ILP, and was thought to be due to vaporised tissue around the fibre-tip because of the high powers used. This tumour was resected because inadequate necrosis was suspected with ILP, and pathological examination confirmed extensive laser-induced necrosis with a peripheral margin of viable tumour. Fine needle biopsy after ILP showed necrotic material in 9 cases, and residual tumour in 2 cases; serum CEA decreased in 7 out of 8 patients after ILP. Twelve out of 16 metastases (1-3.7cm) were said to be completely destroyed. Treatment failure occurred in 4 tumours (sizes 4, 3.9, 3.7, and 2cm), but they were significantly debulked. Minor complications included pain (3 cases), raised temperature (2 cases), and pleural effusion (1
case). At the end of follow-up (7-29 months) 10 out of 11 patients had recurrent tumour separate from the treated sites.

The clinical work on ILP has involved small numbers of patients and the techniques used have varied considerably. Ultrasound has shown thermal tissue changes as seen experimentally, and CT after ILP has shown low density non-enhancing areas at the treatment sites. Biopsies of these areas have confirmed necrotic tissue, but no attempt has been made to perform a detailed correlation of changes seen on imaging with proven pathological necrosis, in the clinical setting. This would be difficult to achieve, and Nolsoe et al (1993) have reported the only case of a liver tumour excised after ILP, confirming extensive necrosis. The fibre-tip modifications applied in the clinical cases reported above should ideally be compared experimentally with the bare fibre-tip, and then be used in the clinical setting if they are found to be advantageous; this has rarely been done. Much more clinical evaluation of ILP is needed, and the ability of monitoring modalities to predict the extent of necrosis during and after ILP needs to be assessed.

2.5. CONCLUSIONS

The concept of ILP was introduced in 1983 (Bown), and the technique was applied clinically to liver tumours at laparotomy in 1985 (Hashimoto et al) and percutaneously in 1989 (Steger et al). The first detailed experimental results were reported in 1987 (Matthewson et al) but it is only over the last 2-3 years that several other groups have reported their experimental and clinical experience. There is considerable variation in the techniques and laser parameters used and also in the results obtained, indicating that ILP is still in the stages of evolution. New findings of practical relevance continue to be reported.

It is with careful experimental and clinical work by several groups that ILP will continue to improve. When the technique is optimised and standardised, further evaluation can be performed with controlled clinical trials, most likely to compare ILP with another treatment modality for liver tumours.

There are presently several gaps in the understanding of the factors which result in maximum thermal damage during ILP. These are discussed in the next chapter, together with the aims of this thesis.
CHAPTER 3: CURRENT DEFICIENCIES IN KNOWLEDGE OF ILP, AND AIMS OF THESIS

3.1. Mechanism of action of ILP

3.2. Significance of charring

3.3. Bare fibre-tip core diameter and cladding material

3.4. Laser wavelength and power

3.5. Histological extent of necrosis

3.6. Imaging of ILP

3.7. Clinical experience

3.8. Summary of aims of thesis
On reviewing the experimental and clinical work on ILP to date, it is clear that there are still several important aspects of the technique which need to be clarified. These are summarised below, together with the aims of this thesis.

### 3.1. MECHANISM OF ACTION OF ILP

All of the work on ILP has been based on the assumption that the deeper the penetration of laser light into tissue, the greater the extent of thermal damage. Under these circumstances the fibre-tip would act as a distributed light source, with isotropic scattering and penetration of the light around it, resulting in a spherical volume of tissue necrosis. Surprisingly, no experimental work has been performed to verify whether this theoretical assumption is correct. Many groups have used interstitial laser therapy without questioning its supposed mechanism of action. Indeed, several investigators and fibre-tip manufacturers have dedicated considerable time and money to further this theory by developing and evaluating various diffuser fibre-tips, which are specially designed to increase the surface area from which light is emitted and to avoid any charring around the fibre-tip which would reduce light penetration. Mathematical modelling has also been performed to predict the temperature rises around a fibre-tip, assuming a distributed optical source (Davis et al, 1989).

Steger (1991) did propose an alternative mechanism for ILP. He suggested that after 20-30s charring occurs around the fibre-tip; light is then strongly absorbed in the black char. This focuses the energy immediately around the fibre-tip, which then acts as a point heat source, subsequent necrosis occurring by thermal conduction into surrounding tissue. This alternative explanation for the mechanism of ILP has not been tested in practice.

The experimental section of this thesis provides strong evidence to support this alternative mechanism, that the optical fibre-tip is nearly always acting as "hot-tip" (ie. a point heat source) during ILP, rather than a distributed optical source.

### 3.2. SIGNIFICANCE OF CHARRING

Most of the experimental studies on ILP clearly show that charring does occur fairly consistently around the fibre-tip during ILP. However, its significance is usually ignored, and comments often made about ways of trying to avoid it. Matthewson et al (1987) found charring to be universally present at powers greater than 1.5W. Steger et al (1992) also had significant charring around each of 4 fibre-tips from a 1x4 coupler, at a power of 1.5W per fibre. Nolsoe et al (1992) even showed the presence of central cavitation and marked
charring around a diffuser fibre-tip, the latter almost always being designed to avoid charring.

Char formation around the optical fibre-tip is clearly an important aspect of ILP, but its exact role and potential have not been addressed. In this thesis the relationship between the presence of charring and the extent of necrosis induced by ILP will be evaluated, and the value of pre-charring the fibre-tip prior to ILP will be assessed. The factors which cause charring will also be explored.

3.3. BARE FIBRE-TIP CORE DIAMETER AND CLADDING MATERIAL

An optical fibre typically has a silica core surrounded by a cladding, with an outer covering of a jacket or buffer coat. The cladding is made of plastic, silica, or hard polymer. Although the size of the fibre core is usually quoted in the literature dealing with ILP, the cladding material is rarely, if ever, mentioned. Furthermore, many investigators seem to confuse the jacket/buffer coat and the cladding. The distal few millimetres of the jacket/buffer coat and sometimes also the cladding are frequently removed prior to ILP. However, it is usually not clear whether only the jacket/buffer coat is removed, or the cladding stripped off as well. The presence or absence of fibre-tip cladding may influence the size of necrosis produced by ILP; if the cladding is left intact, the type of material of which it is made may also affect the size of necrosis.

These factors, together with the influence of the diameter of the optical fibre on ILP-induced necrosis have not previously been evaluated, and will be addressed in this thesis.

3.4. LASER WAVELENGTH AND POWER

Since the 1064nm Nd:YAG laser gives the deepest tissue penetration, it has been assumed to be the optimal wavelength for ILP. However, this assumption has not been tested in practice, and no other laser wavelength has been evaluated. The effect of several different, less penetrating wavelengths on ILP will be investigated. These include the 1320nm Nd:YAG, the 805nm diode, and the 488nm/514nm Argon laser wavelengths.

Several studies have shown that at powers above 3W, the necrosis produced by ILP is ellipsoidal in shape, and its longitudinal length can be quite variable and unpredictable. A new method of safely increasing the power applied during ILP is suggested and evaluated in this thesis. This involves attaching a segment of metal needle to the fibre-tip, and so focusing all of the laser light to heat the needle. Necrosis then occurs entirely by thermal conduction, and its longitudinal length is limited and controlled by the length of the needle
segment; the transverse length of necrosis should then increase by increasing the power and energy delivered

3.5. HISTOLOGICAL EXTENT OF NECROSIS

Several authors have described the histological features of ILP-induced necrosis using standard haematoxylin and eosin (H & E) staining. Since ILP can produce necrosis with or without tissue charring around the fibre-tip with a somewhat different mechanism (the fibre-tip acting as point heat source or distributed optical source), the histological features may differ in the presence or absence of charring. Also, H & E staining may not define the true extent of necrosis, and it is possible that morphologically normal but non-viable cells exist outside the boundaries of necrosis seen on H & E staining. Histochemical staining for intracellular enzymes, would differentiate viable from non-viable cells even if they appear normal on H & E staining.

The histological features of charred and uncharred necrotic lesions will be evaluated in this thesis, and the extent of necrosis defined by histochemical staining compared to that seen on H & E staining.

3.6. IMAGING OF ILP

Ultrasound has shown thermal damage during ILP in normal animal liver experimentally, and in tumours clinically, as an expanding echogenic zone. Although it has not been evaluated to differentiate treated from untreated tumour on follow-up scans, it is unlikely to be useful. Experimental work has also been performed using MRI to monitor thermal changes during ILP and evaluate the extent of necrosis afterwards. Further work is still needed in different tissues (particularly liver), and a methodical approach to sequence optimisation for imaging laser-induced thermal damage in vivo is required.

No experimental work has been done to assess CT in the animal model, even though clinically, dynamic contrast enhanced CT is thought to be a useful modality for differentiating treated from untreated tumour after ILP (Masters et al, 1990). The changes seen on dynamic CT which are thought to represent laser-induced necrosis need to be evaluated experimentally, and an imaging-pathologic correlation performed, in order to confirm that the extent of these changes on CT correspond to the extent of necrosis pathologically. Furthermore, the optimal CT technique (non-contrast, dynamic or delayed scanning) and the optimal time to perform CT after ILP need to be evaluated.
The role of CT in ILP will be addressed in the experimental and clinical section of this thesis.

3.7. CLINICAL EXPERIENCE

Although some clinical work using ILP to treat liver tumours has already been reported, experience is still very limited. Further clinical evaluation of ILP will be presented in this thesis. It will be attempted to define the selection criteria for ILP, based on a detailed analysis of the results obtained from an assessment of patient outcome and tumour destruction.

The role of ultrasound, CT and MRI will be critically assessed in the clinical setting, and the potential advantages and disadvantages of each modality determined.

The areas which present problems with the clinical application of ILP will be highlighted, and ways of improving the technique will be sought.

3.8. SUMMARY OF AIMS OF THESIS

1. To clarify the mechanism of action of ILP.

2. To safely increase the extent of necrosis around a fibre-tip by evaluating:
   (a) Fibre-tip core diameter and cladding material
   (b) Pre-charred fibre-tips
   (c) Different laser wavelengths
   (d) Metal needle-tips

3. To accurately assess the extent of necrosis by:
   (a) Histopathological and histochemical evaluation
   (b) Performing a CT-pathologic correlation

4. To evaluate the clinical application of ILP, determine selection criteria for patients, and perform a critical assessment of the imaging methods used.
SECTION B: EXPERIMENTAL WORK

CHAPTER 4: EVALUATION OF FIBRE-TIPS AND LASER WAVELENGTHS.

CHAPTER 5: ASSESSMENT OF EXTENT OF NECROSIS FOLLOWING ILP.
CHAPTER 4: EVALUATION OF FIBRE-TIPS AND LASER WAVELENGTHS

4.1. Introduction

4.2. Methods
   4.2.1. Technique of ILP
   4.2.2. Assessment of necrosis
   4.2.3. Fibre-tip core diameter and cladding
   4.2.4. Laser wavelengths
   4.2.5. Pre-charred fibre-tips
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4.3. Results
   4.3.1. Surface effects and necrotic lesion
   4.3.2. Fibre-tip core diameter and cladding
   4.3.3. Laser wavelengths
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4.4. Discussion
   4.4.1. Rat liver model for ILP
   4.4.2. Significance of charring
   4.4.3. Factors which cause charring
   4.4.4. Role of pre-charred fibre-tips
   4.4.5. Optimal laser wavelength for ILP
   4.4.6. Optimal power for ILP
   4.4.7. Potential of metal needle-tips
   4.4.8. Perivascular necrosis: an important new finding
   4.4.9. Conclusions
4.1. INTRODUCTION

This chapter deals with the experimental evaluation of different optical fibres and laser wavelengths. During preliminary work using bare optical fibres, it became apparent that the size of necrosis following ILP was related to the type of fibre used. This prompted a study comparing fibres of different diameters and different cladding material. The results of this study showed a strong association between the size of charring around the fibre-tip and the extent of necrosis. This suggested that the presumed theoretical advantage of the deeply penetrating Nd:YAG 1064nm wavelength may not be true, in practice. Therefore, several less penetrating wavelengths were evaluated; these included the 1320nm Nd:YAG, the 805nm GaAlAs diode, and the 488nm/514nm Argon laser wavelengths. These studies confirmed the correlation between charring and necrosis. A further study was then conducted using pre-charred fibre-tips, to see if these consistently produced greater necrosis compared to clean fibre-tips.

The benefits of focusing the laser energy immediately around the fibre-tip were taken to the extreme by attaching a segment of a metal needle to the fibre-tip and sealing its distal end, so that all of the laser energy was used to heat the metal needle; these experiments were carried out in rat and pig liver, in vivo.

4.2. METHODS

4.2.1. TECHNIQUE OF ILP

Wistar rats (weight 250-300g) were anaesthetised using a combination of intra-muscular Hypnorm (Janssen Pharmaceuticals Ltd, Oxford, UK) and diazepam (0.5ml/kg and 2mg/kg, respectively). A laparotomy was performed using a midline incision, and the middle hepatic lobe brought out onto the anterior abdominal wall. An optical fibre was connected to the chosen laser, and the appropriate laser parameters (power and exposure time) were set; the power output was checked using a coherent power meter (Model 201, Coherent UK, Cambridge, England). Mode scrambling of the optical fibre being investigated was performed in order to have a uniform light beam profile at its output end. The fibre-tip was then inserted into the liver so that at least 1cm of its distal end was embedded in the tissue, and the aiming beam easily seen through the liver surface (Figure 4.1). The laser was then activated for the duration of the pre-selected exposure time.

4.2.2. ASSESSMENT OF NECROSIS

During ILP, visible changes to the liver surface, and any reduced intensity or disappearance of the red aiming beam (He-Ne, 633nm, 2mW) were noted. At the end of
the exposure time, the fibre was removed, sutures were placed on the right and left edge of the liver lobe, so that a line joining the sutures corresponded to the line of insertion of the optical fibre; the liver lobe was then replaced in the abdomen, and the wound closed. The fibre-tip was inspected and the power re-checked. The rat was sacrificed 24hrs later, and the treated lobe of liver resected and placed in 10% buffered formalin. Two days later, the liver was carefully sectioned into 1-2mm slices and the maximum transverse width (perpendicular to the fibre track) and longitudinal length (along the fibre track) of the necrosis and charring measured (Figure 4.2).

4.2.3. FIBRE-TIP CORE DIAMETER AND CLADDING

4.2.3.1. Bare optical fibres
There are 3 types of optical fibres for medical use - their main difference is in the type of cladding around the core. The construction of a typical optical fibre is shown in Figure 4.3. The core of all 3 types of fibres is made of fused silica, and it is the diameter of the core which is normally quoted (0.2-0.6mm). The buffer coat or jacket of the fibre is usually made of nylon or acrylate (0.1-0.2mm thick), but it is the cladding material (0.02-0.1mm thick) which is the distinguishing feature of the different fibres. The cladding may be plastic, hard polymer, or silica. Plastic cladding is soft and easily damaged if care is not taken when removing the buffer coat/jacket; it can also be removed chemically or mechanically scraped off the core. Silica cladding is hard, not easily damaged, and very difficult to remove from the fibre core. Hard polymer cladding has properties lying between plastic cladding and silica cladding.

This study compares plastic clad fibres with silica clad ones, as well as 0.2mm core diameter fibres with 0.4mm core diameter ones. All fibres were plane cleaved and their distal 3mm of buffer coat/jacket stripped prior to performing ILP in each rat.

4.2.3.2. Comparison of a 0.2mm plastic clad fibre with a 0.4mm silica clad fibre
This was the preliminary study which led to the more detailed comparative work (section 4.2.3.3). The laser used for this study was a 1064nm Nd:YAG laser (CVI, Albuquerque, New Mexico, USA). A fixed laser power of 2W and exposure time of 500s (energy 1000J) were used to induce necrotic lesions in 10 rat livers, in vivo. Five lesions were produced with a 0.2mm plastic clad fibre, and 5 with a 0.4mm silica clad fibre. The stripping of the buffer coat/jacket off the distal 3mm of fibre was technically more difficult with the smaller plastic clad fibre. It is highly likely that the plastic cladding was damaged, although this was not the intention.
Figure 4.1: (a) ILP of rat liver, with the optical fibre embedded in the liver, just prior to ILP. (b) A closer view shows the red HeNe aiming beam, visible through the liver surface.
Figure 4.2: Diagram of measurements made on the fixed lobe of liver. a=transverse width of necrosis, b=longitudinal length of necrosis.

Figure 4.3: Diagram of a typical optical fibre. (Not to scale).
4.2.3.3. Comparison of fibre core diameter (0.2mm vs 0.4mm) and cladding type (plastic vs silica)
This work was performed following the results of the preliminary study (see section 4.3.2.1). Since it was clear that the 0.2mm plastic clad fibre gave larger necrotic lesions than the 0.4mm silica clad fibre, it was decided to intentionally strip the cladding, as well as the buffer coat, off the distal 3mm of the plastic clad fibre. The objective was to see if by removing the cladding, the difference in lesion size is eliminated. The plastic cladding was mechanically stripped with a sharp blade.

Thirty two rats had ILP performed to their liver. In 16 rats the plastic clad (cladding stripped) fibres were used, 0.2mm in 8 rats and 0.4mm in the other 8. Silica clad fibres (cladding intact) were used in the remaining 16 rats, 0.2mm in 8 rats and 0.4mm in the other 8. For each type of fibre the power used was kept fixed at 2W, but the exposure time was either 100s or 500s (energies 200J or 1000J). Four lesions were produced at each energy setting.

4.2.4. LASER WAVELENGTHS

Thirty nine Wistar rats were used for this experiment. The laser wavelengths investigated were 1064nm Nd:YAG, 1320nm Nd:YAG, 805nm diode, and 488nm/514nm Argon. The lasers used were: a dual wavelength (1064nm and 1320nm) Nd:YAG laser (Multilase 2100, Technomed, France); a new high power diode (805nm) laser (Diomed-25, Diomed, Cambridge, UK); an Argon ion laser (Aurora, Cooper Medical, Santa Clara, CA). A 0.4mm core diameter optical fibre was used for all wavelengths. With the Multilase Nd:YAG laser it was only possible to use the optical fibre supplied with the laser, and this was a hard polymer clad fibre; both the 1064nm and 1320nm wavelengths were evaluated with the same laser and optical fibre. For the diode and Argon laser work a silica clad fibre was used. Only the buffer coat/jacket was removed from the fibre-tips, the cladding left intact in all cases. The powers used at each wavelength were 1W, 2W, and 3W, and the corresponding exposure times were 1000s, 500s and 333s, respectively, the energy kept constant at 1000J; for the Argon laser the maximum output was 2.5W, and so only powers of 1W and 2W were assessed. At least three lesions were produced at each power setting and wavelength.

4.2.5. PRE-CHARRED FIBRE-TIPS

Eighteen Wistar rats had ILP performed using the two Nd:YAG laser wavelengths (1064nm and 1320nm) from the Multilase laser. A 0.4mm hard polymer clad fibre was fired with the tip dipped into a drop (approximately 0.1ml) of rat blood at 4-5W for a few seconds so that the distal 3mm of the fibre-tip was blackened. Any excess debris was gently wiped off the fibre-tip before inserting it into the rat liver. The laser power was set
at the desired level of 1W, 2W or 3W (energy 1000J) before commencing ILP. Three rats were used for each power setting and wavelength. The results obtained at the two Nd:YAG wavelengths using pre-charred fibre-tips were compared to the corresponding results with a clean fibre-tip (from section 4.2.4.).

4.2.6. METAL NEEDLE-TIPS

4.2.6.1. Short (5mm) metal needle versus bare fibre in rat liver
A 0.4mm silica clad fibre was plane cleaved and its distal 3mm of buffer coat/jacket stripped, leaving the cladding intact. A 5mm segment of a standard 21 gauge steel needle was cut, and the distal 3mm of the fibre-tip inserted into this. The proximal end of the needle was "crimped" onto the fibre, and the distal end of the needle was squeezed with a clamp so that no laser light could escape from the metal needle segment.

Nine Wistar rats had ILP performed as described above. The laser used was the Multilase Nd:YAG at a wavelength of 1064nm. The fibre with the metal needle-tip was inserted into the rat liver so that at least 1cm of the fibre/needle-tip was embedded within the liver tissue. The powers evaluated were 1W, 2W, and 3W (energy 1000J), with 3 rats used for each power level. After ILP, the fibre was withdrawn from the liver, but the needle segment remained stuck in the liver. The results obtained were compared with the data from section 4.2.4. using clean, bare fibre-tips.

4.2.6.2. Longer metal needles and higher powers in pig liver
This study was done in a larger animal model in vivo, using a more heavily absorbed laser wavelength with which to compare the size of necrosis from metal tips and bare fibre-tips, at higher powers. Also, because the 5mm needle-tip remained stuck to the rat liver after ILP, it was decided to use long metal needles with the optical fibre inserted down the needle, and the tip of the fibre lying 1-3cm proximal to the tip of the needle; this method avoids the problem of securing a segment of needle to the fibre. The tip of the needle was squeezed with a clamp to prevent any light from escaping distally.

Two female Large White pigs (weight 25-30kg) were anaesthetised with intramuscular injections of ketamine (10mg/kg), diazepam (1mg/kg) and atropine (0.3mg), and anaesthesia maintained with halothane/oxygen (initially 4% halothane, then 1.5-2%) via a mask. A midline laparotomy was performed and the left lateral, left central and right central hepatic lobes freed from any ligamentous attachment and brought forward onto the anterior abdominal wall. The portable semiconductor laser was used (Diomed-25, Diomed, Cambridge, UK), and a standard 0.4mm optical fibre (supplied with the laser) which was hard polymer clad. The optical fibre was plane cleaved, and the distal 3mm of buffer coat stripped, leaving the cladding intact around the fibre-tip. The metal needle
used was a 20cm long 19 gauge steel needle (William Cook Europe, Bjaeverskov, Denmark).

In the first pig 12 necrotic lesions were produced in the 3 lobes of liver, 6 with the bare fibre and 6 with the metal needle. Powers of 2W and 4W were used with exposure times of 500s and 250s, respectively, keeping the energy constant at 1000J; 3 lesions were produced at each power/time setting. At 2W the needle or bare fibre were inserted 2.5cm into the pig liver lobe, and at 4W they were inserted 3.5cm into the liver; a flag made from sterile tape was attached to the needle or fibre to indicate the depth of insertion. For the needle experiments, the optical fibre was inserted into the needle so that the tip of the fibre lay 1cm proximal to the tip of the needle.

In the second pig, a much higher energy of 4000J was used to see if the size of necrosis increased; the powers used were 4W and 8W, for 1000s and 500s, respectively. Seven necrotic lesions were produced, three at 4W and metal needle, three at 8W and metal needle, and one at 8W and bare fibre. At 4W the needle was initially inserted 4cm into the liver, and then 6cm for the next two lesions; the fibre-tip was 1cm proximal to the needle-tip. At 8W the needle was initially inserted 6cm into the liver, and then 7cm for the next two lesions; the fibre-tip was placed 3cm, 2cm, and 1cm proximal to the needle-tip (this was varied in order to assess forward conduction of heat along the needle).

During ILP with the metal needle, the hub of the needle was gently rotated every 5-10s to prevent any charred tissue sticking to the needle. Sutures were placed at the point of needle/fibre entry into the liver lobe in order to define the plane for subsequent sectioning. After ILP, the extent of char and blackening on the needle-tip was noted, and the fibre-tip was inspected for damage. The liver lobes were returned to the abdominal cavity, the wound closed and the pigs allowed to recover fully.

Both pigs were sacrificed 48hrs after ILP, by using sedation followed by carbon dioxide inhalation. The liver lobes which had been treated were resected and fixed in formalin for 3-4 days. They were then sectioned into 2-3mm slices parallel to the plane of the needle/fibre track, and the maximum size of the necrotic lesion measured in 3 planes - along the line of the fibre-track and in 2 perpendicular planes indicating the width and depth of the necrotic lesion.

4.2.7. STATISTICAL ANALYSIS

For comparative purposes, the mean transverse width (and range in brackets) of necrosis and charring of the different groups are included in the text. All individual measurements of each necrotic lesion (transverse and longitudinal) are given in the appendix. For the
Argon laser and metal needle-tip data, the mean longitudinal length of necrosis, as well as the transverse width, is quoted in the text.

Because of the small sample sizes (3, 4 or 5 rats in each group), only the means and ranges of each group are given in the text; a better idea of the dispersion of the data in each group can be gauged by looking at the individual measurements (3-5 per group) in the appendix.

In view of the small sample sizes, a normal distribution of the data could not be assumed, and so non-parametric statistical analyses were used for significance testing. The Wilcoxon rank sum test for two independent samples was used to compare the means of two groups, and statistical significance taken at the 5% level. However, this test was only performed in those cases where there was a clear difference between the means of two groups, which was thought to be of practical and clinical relevance; this amounted to a difference of at least 5mm. In such cases, inspection of the raw data (in the appendix) shows an obvious difference between these groups, and statistical testing was performed to emphasise this difference and allow clearer presentation of the data in the text.

The association between the size of necrosis and the size of charring was displayed on a scatter diagram, and tested statistically by calculating Kendall’s rank correlation coefficient (tau).

4.3. RESULTS

All of the individual measurements (transverse width and longitudinal length) are given in the appendix, and their means and ranges are presented in the following sections.

4.3.1. SURFACE EFFECTS AND NECROTIC LESION

During ILP, the changes that were seen on the surface of the liver lobe included drying, blackening and distortion. The red He-Ne aiming beam could easily be seen through the liver surface at the onset of ILP, and often diminished in intensity during exposure; the timing of its disappearance was strongly associated with the final extent of necrosis - the quicker the light disappeared, the larger the necrotic lesion and the greater the likelihood of charring being present around the fibre-tip. When there was no or minimal loss of aiming beam intensity, there was also no tissue charring present. With the Argon laser, there was no aiming beam, and the visible blue/green light which this laser emits could not be seen through the liver surface, at the onset of ILP.
On resecting the treated rat liver lobe 24hrs after ILP, a well-defined zone of yellow coagulative necrosis was clearly visible on the surface (Figure 4.4); this appeared roughly circular. In some lesions (usually those greater than 15mm in diameter), a wedge of infarcted liver was also seen extending from part of the necrosis to the liver edge - this did not preclude an estimation of the size of necrosis, since this wedge of infarction always arose from less than half of the circumference of the laser-induced necrosis. Also, the wedge infarction was usually a more pale yellow in appearance. Therefore, the full circumference of the necrosis could be approximately mapped out.

On sectioning the liver lobe, the transverse width and longitudinal length of necrosis were approximately the same. The exception to this was the necrosis produced by the Argon laser at a power of 2W (see below). The charring, if present, was also approximately symmetrical in all lesions produced by the 1064nm Nd:YAG laser. However, the longitudinal length of charring was significantly greater than the transverse width in lesions produced by the 1320nm Nd:YAG, 805nm diode, and all pre-charred fibre-tips, at powers of 2W or 3W; this phenomenon was seen with the Argon laser at 1W and 2W.

Therefore, the data presented below mainly represents the transverse width of necrosis and charring, for comparative purposes.

The typical appearances of sectioned rat liver lobe from a charred and uncharred necrotic lesion are shown in Figure 4.5.

4.3.2. FIBRE-TIP CORE DIAMETER AND CLADDING

With the silica clad fibres, there were mild surface effects and the intensity of the aiming beam transmitted through the tissue had diminished noticeably after 500s, and occasionally disappeared after 100-200s. With plastic clad fibres (cladding intact or removed), there were more marked surface effects, with complete loss of aiming beam light by 50-100s.

4.3.2.1. Plastic clad (0.2mm) versus silica clad (0.4mm) fibres
The 0.2mm plastic clad fibre (cladding intact) produced significantly greater necrosis and charring than the 0.4mm silica clad fibre (Table 4.1).

4.3.2.2. Further evaluation of fibre-tip diameter and cladding
The sizes of necrosis and charring produced by 0.2mm and 0.4mm plastic clad (cladding removed from tip) and silica clad fibres are summarised in Tables 4.2 and 4.3.
Figure 4.4: Lobe of rat liver 24hrs after ILP, showing a well-defined zone of coagulative necrosis. The sutures represent the direction of the optical fibre.

Figure 4.5: Sections of rat liver 24hrs after ILP, showing an uncharred (above) and charred (below) necrotic lesion. The uncharred lesion appears fairly homogeneous, whereas the charred lesion has a large central zone of tissue blackening at the site of the fibre-tip.
Table 4.1: Mean (range) transverse width (mm) of necrosis and charring produced by a 0.2mm plastic clad fibre and a 0.4mm silica clad fibre, in rat liver, using a power of 2W for 500s (energy 1000J).

<table>
<thead>
<tr>
<th></th>
<th>0.2mm plastic clad fibre</th>
<th>0.4mm silica clad fibre</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Necrosis</strong></td>
<td>17.0 (15-20)</td>
<td>8.0 (6-10)</td>
</tr>
<tr>
<td><strong>Charring</strong></td>
<td>3.2 (2-4)</td>
<td>0.4 (0-1)</td>
</tr>
</tbody>
</table>

Table 4.2: Mean (range) transverse width (mm) of necrosis from different fibres at 200J and 1000J (power 2W).

<table>
<thead>
<tr>
<th></th>
<th>200J</th>
<th>1000J</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>0.2mm silica</strong></td>
<td>5.0 (4-6)</td>
<td>9.5 (7-12)</td>
</tr>
<tr>
<td><strong>0.4mm silica</strong></td>
<td>5.3 (4-7)</td>
<td>10.0 (7-12)</td>
</tr>
<tr>
<td><strong>0.2mm plastic</strong></td>
<td>9.5 (8-10)</td>
<td>16.8 (15-16)</td>
</tr>
<tr>
<td><strong>0.4mm plastic</strong></td>
<td>5.8 (5-7)</td>
<td>16.3 (15-18)</td>
</tr>
</tbody>
</table>

Table 4.3: Mean (range) transverse width (mm) of charring from different fibres at 200J and 1000J (power 2W).

<table>
<thead>
<tr>
<th></th>
<th>200J</th>
<th>1000J</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>0.2mm silica</strong></td>
<td>0</td>
<td>1.0 (0-2)</td>
</tr>
<tr>
<td><strong>0.4mm silica</strong></td>
<td>0</td>
<td>0.5 (0-1)</td>
</tr>
<tr>
<td><strong>0.2mm plastic</strong></td>
<td>1.3 (0-2)</td>
<td>3.0 (2-4)</td>
</tr>
<tr>
<td><strong>0.4mm plastic</strong></td>
<td>0</td>
<td>2.4 (1.5-3)</td>
</tr>
</tbody>
</table>
The data from Tables 4.2 and 4.3 can be summarised as follows:
(a) There was no significant difference in necrosis size between the 0.2mm and 0.4mm silica clad fibres at the low or high energy used.
(b) There was no significant difference in necrosis size between the 0.2mm and 0.4mm plastic clad (cladding removed from tip) fibres at the higher energy. At the lower energy, the 0.2mm plastic fibre gave greater necrosis than the 0.4mm plastic fibre, but the size of the difference was not of practical relevance.
(c) The 0.2mm and 0.4mm plastic clad fibres (cladding removed from tip) gave significantly greater necrosis than the corresponding silica clad (cladding intact) fibres, at the higher energy (p<0.05).
(d) The size of necrosis showed a strong positive correlation with the size of charring (tau=0.654, p<0.001). A scatter diagram of this data is shown in Figure 4.6.

4.3.2.3. Fibre-tip damage and power loss after ILP
If the aiming beam remained visible throughout the procedure, and in the absence of charring, the fibre-tip was clean after ILP. However, in the presence of charring the fibre-tip was invariably damaged following ILP; there was usually some resistance to removing it from the liver, and there was always either tissue debris stuck to it, or some black char around the side of the fibre-tip. The fibre-tip was always intact, and no part of it was broken or left inside the liver lobe. The embedded buffer coat/jacket was also sometimes burnt. The degree of blackening or tissue debris on the fibre-tip was variable, but the distal 1mm of the fibre-tip was always free of any char (Figure 4.7).

If charring was present, light was frequently seen to be emitted laterally, ie. out of the sides of the damaged fibre core. A power loss of up to 0.8W was observed after ILP, probably due to this effect.

4.3.3. LASER WAVELENGTHS
During ILP with the 1064nm Nd:YAG laser, only mild surface effects were seen with localised swelling and some diminution of the He-Ne aiming beam after 200-500s. With the 1320nm Nd:YAG laser, there was blackening, swelling and distortion of the liver surface, with complete loss of the He-Ne aiming beam by 15-60s. More marked surface effects occurred with the 805nm laser, with loss of the aiming beam by 10-20s; mini-explosions were also heard at 2W and 3W but not at 1W, and on two occasions (power 3W) the liver surface ruptured with considerable smoke production. With the Argon laser (488/514nm), mini-explosions were consistently heard, associated with marked surface effects; at 2W, the laser light beam was clearly propagating forwards fairly rapidly in the liver tissue, reaching the liver surface (at the edge of the lobe) in 20-30s. The blue/green light was then seen breaching the liver capsule, with considerable loss of smoke. Hence, most of the energy during Argon laser ILP, was not delivered to the liver lobe.
After ILP at each wavelength, the appearance of the fibre-tip and the power loss were similar to those described above, in section 4.3.2.3.

The sizes of necrosis and charring produced by the 1064nm Nd:YAG, 1320nm Nd:YAG and 805nm diode lasers, at powers of 1W, 2W and 3W, are summarised in Tables 4.4 and 4.5. Table 4.6 gives the data for the 488/514nm Argon laser separately because only part of the delivered energy was used to create the lesions; also, since the necrotic lesion was ellipsoidal, the longitudinal as well as the transverse sizes of necrosis and charring are given for the Argon laser experiments.

Table 4.4: Mean (range) transverse width (mm) of necrosis from 1064nm, 1320nm and 805nm wavelengths, and powers of 1W, 2W and 3W (constant energy, 1000J).

<table>
<thead>
<tr>
<th>Wavelength</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1W</td>
</tr>
<tr>
<td>1064nm</td>
<td>3.4 (0-6)</td>
</tr>
<tr>
<td>1320nm</td>
<td>13.0 (11-14)</td>
</tr>
<tr>
<td>805nm</td>
<td>10.3 (8-13)</td>
</tr>
</tbody>
</table>

Table 4.5: Mean (range) transverse width (mm) of charring from 1064nm, 1320nm and 805nm wavelengths, and powers of 1W, 2W and 3W (constant energy, 1000J).

<table>
<thead>
<tr>
<th>Wavelength</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1W</td>
</tr>
<tr>
<td>1064nm</td>
<td>0</td>
</tr>
<tr>
<td>1320nm</td>
<td>0.8 (0.5-1)</td>
</tr>
<tr>
<td>805nm</td>
<td>3.0 (1-7)</td>
</tr>
</tbody>
</table>
Table 4.6: Mean transverse width (T) and longitudinal length (L) (mm) of necrosis and charring from 488nm/514nm Argon laser, at powers of 1W and 2W (energy 1000J). The individual measurements are given in the appendix (page 207).

<table>
<thead>
<tr>
<th>Power</th>
<th>1W</th>
<th>2W</th>
</tr>
</thead>
<tbody>
<tr>
<td>Necrosis</td>
<td>T</td>
<td>L</td>
</tr>
<tr>
<td>13.7</td>
<td>14.3</td>
<td>16.3</td>
</tr>
<tr>
<td>Charring</td>
<td>2.7</td>
<td>5.3</td>
</tr>
</tbody>
</table>

These tables show:
(a) The 1320nm Nd:YAG and 805nm diode lasers give significantly greater necrosis than the 1064nm Nd:YAG laser, at the powers used (p<0.05).
(b) For practical purposes, there is no significant difference in the size of necrosis produced by the 1320nm Nd:YAG and 805nm diode lasers.
(c) There is a significant increase in necrosis size when increasing the power from 1W to 2W (p<0.05), but there is a plateau effect from 2W to 3W, at all three wavelengths.
(d) Combining the data from Tables 4.4 and 4.5, and comparing the size of necrosis with the size of charring gives a correlation coefficient, $\tau=0.623$ (p<0.001). This is consistent with the similar analysis of the fibre-tip data (Figure 4.6). The wavelength data is presented as a scatter diagram in Figure 4.8.
(e) Table 4.6 shows that even though only part of the energy delivered by the Argon laser was used to induce the necrosis, the transverse width of necrosis at 1W and 2W was still significantly greater than that produced by the 1064nm Nd:YAG wavelength (p<0.05).

4.3.4. PRE-CHARRED FIBRE-TIPS

The surface effects were similar to those described for the 1320nm Nd:YAG laser using a clean fibre-tip. Table 4.7 gives the size of necrosis obtained from pre-charred fibre-tips; the corresponding sizes of charring are given in the appendix. Comparing this data with that using clean fibre-tips (Table 4.4), it is clear that at the 1064nm Nd:YAG wavelength, the mean size of necrosis increases significantly with the pre-charred fibre-tips at all three powers used (p<0.05); this was by a factor of 4.5, 1.7 and 1.9 at powers of 1W, 2W and 3W, respectively. However, at the 1320nm wavelength, pre-charred fibre-tips made no significant difference to the size of necrosis compared to clean fibre-tips. The pre-charred fibre-tip at 1064nm and 2W appears to produce smaller lesions than those from the 1320nm and 805nm at 2W, although this is not the case at 1W and 3W.
Figure 4.6: Scatter diagram of transverse width of necrosis versus charring, based on 42 pairs of measurements from the fibre-tip data. Correlation coefficient, \( \tau = 0.654 \) (\( p < 0.001 \)).

Figure 4.8: Scatter diagram of transverse width of necrosis versus charring, based on 33 pairs of measurements from the wavelength data. Correlation coefficient, \( \tau = 0.623 \) (\( p < 0.001 \)).
Table 4.7: Mean (range) transverse width (mm) of necrosis using a pre-charred fibre-tip and 1064nm or 1320nm wavelengths. Powers of 1W, 2W and 3W were used with an energy of 1000J.

<table>
<thead>
<tr>
<th>Wavelength</th>
<th>Power</th>
<th>1W</th>
<th>2W</th>
<th>3W</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1W</td>
<td>15.3 (14-17)</td>
<td>14.7 (12-17)</td>
<td>18.7 (17-21)</td>
</tr>
<tr>
<td>1064nm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1320nm</td>
<td>2W</td>
<td>12.0 (10-13)</td>
<td>20.7 (19-21)</td>
<td>19.3 (18-20)</td>
</tr>
<tr>
<td></td>
<td>3W</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4.3.5. METAL NEEDLE-TIPS

4.3.5.1. Short (5mm) metal needle vs. bare fibre in rat liver
During ILP with the bare fibre-tip (1064nm, Nd:YAG), only mild effects of drying and slight blackening were noted on the surface of the rat liver lobe. With the metal needles, the surface effects were much more marked: at 1W there was a controlled and gradually expanding zone of tissue drying and blackening around the site of the needle-tip; at 2W several small mini-explosions were heard, with a rapid expansion of the blackened zone, appearance of charring at the site of the needle-tip, and dissipation of smoke from this charred area; at 3W the effects were dramatic, with rupture of the liver surface in 2 cases and marked emission of smoke - the needle-tip was visible through the liver surface, and it appeared red hot with a cavity around it. As mentioned in the methods, on withdrawing the fibre/needle-tip combination at the end of ILP, the needle-tip segment was always left behind, firmly stuck to the charred tissue.

On resecting the treated liver lobe 24hrs after ILP, a small well-defined, roughly circular zone of yellow coagulative necrosis was seen on the surface of the lobes treated by the bare fibre; no charring or cavitation was present on sectioning. The lobes treated by the metal needles clearly had much more extensive necrosis, frequently extending very close to the edge of the liver lobe, and associated with marked charring and some cavitation around the metal needle-tips; the shape of the necrosis on the liver surface was again roughly circular. The mean extent of necrosis along (longitudinal) and perpendicular (transverse) to the track of the fibre are given in Table 4.8, for the bare fibre-tip and metal needle-tip.
Table 4.8: Mean longitudinal length (L) and transverse width (T) (mm) of necrosis in a lobe of rat liver, following ILP with a 5mm segment of a metal needle-tip, at an energy of 1000J. The individual measurements are given in the appendix (page 208).

<table>
<thead>
<tr>
<th>Power</th>
<th>Necrosis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>L</td>
<td>T</td>
</tr>
<tr>
<td>1W</td>
<td>17.7</td>
<td>15.7</td>
</tr>
<tr>
<td>2W</td>
<td>18.3</td>
<td>18.3</td>
</tr>
<tr>
<td>3W</td>
<td>18.0</td>
<td>17.3</td>
</tr>
</tbody>
</table>

4.3.5.2. Longer metal needles and higher powers in pig liver
This data represents a preliminary evaluation of the parameters used. Some of the results were unexpected, and their description is unavoidably lengthy. The data does provide interesting and useful information about the potential of metal needle-tips.

No similar surface effects to the rat liver were seen, because of the much larger liver, and the depth of insertion of the needle/fibre-tips.

In the first pig, after ILP at 2W and 1000J, the needle-tip was blackened along a 10mm segment, but the distal 5mm of the tip was clean (fibre-tip was 1cm proximal to needle-tip). This pattern was seen in 2 of the lesions created, and in one of these there was tissue debris 3mm thick surrounding the blackened segment after withdrawal of the needle (in this case there had been a 50s inadvertent delay before rotating the hub of the needle, thus allowing the charred tissue debris to stick to the metal). In the third lesion produced at 2W with the metal needle, the distal 15mm of the needle was clean, and only a 4mm blackened segment was present proximal to this (it was later discovered, on sectioning the liver, that this lesion was adjacent to a large blood vessel). The bare fibres at 2W, had 5mm, 6mm and 3.5mm of their cladding burnt off the distal fibre after ILP (again, with the shortest of these, 3.5mm, the fibre-tip lay adjacent to another blood vessel). At 4W and 1000J, the needle-tip was blackened along a 20-25mm segment, with the distal 5-8mm of the tip being clean (fibre-tip was 1cm proximal to needle-tip); this pattern was seen after all 3 lesions created at 4W (Figure 4.9). The bare fibres at 4W had 11, 11 and 7mm of their cladding burnt off the distal fibre after ILP.
Figure 4.7: Fibre-tips after ILP, showing variable appearance of char (arrows) around two tips. The fibre-tip on the left is a clean tip before ILP.

Figure 4.9: Metal needle after ILP in pig liver, using 4W for 250s. The sterile flag to indicate the depth of insertion can be seen, 35mm from the needle-tip. There is a 20mm segment of blackening, due to a layer of charred tissue debris, and the distal 8mm of the tip is clean, indicating that little, if any heat was conducted forwards.
On sectioning the liver lobes of the first pig, the necrosis was seen as a pale spherical or ellipsoidal zone around a length of central charring. The bare fibre-tip produced more spherical lesions compared to more ellipsoidal ones with the metal needles; the necrosis and charring was shorter and wider with the bare fibres, but longer and more narrow with the metal needles (Figures 4.10 and 4.11). In 2 cases (one metal needle and one bare fibre) the necrosis was adjacent to large vessels, in which the flowing blood had a cooling effect with subsequently smaller lesions (Figure 4.12). In another 2 cases (again one metal needle and one bare fibre), there was tracking of necrosis away from the main necrotic lesion, along and around small vessels passing through. This extended for about 1cm away from the main necrotic lesion, and was more prominent if the traversing vessel was smaller - these vessels were thrombosed (Figure 4.13).

Table 4.9 shows the mean dimensions of the necrotic lesions produced at 2W and 4W (bare fibre and metal needle), and the mean estimated volumes of necrosis (not including the 2 lesions abutting large blood vessels, described above). It can be seen that the metal needle produces longer but narrower necrotic lesions. At 2W the mean volume of necrosis induced by the metal needle is only half of that produced by the bare fibre, although at 4W this difference is less marked.

Table 4.9: Mean dimensions (mm) of necrotic lesions produced by a bare fibre and a metal needle in pig liver, at 2W and 4W (energy constant at 1000J). L = longitudinal length of necrosis along fibre/needle track, T = transverse width of necrosis, D = depth of necrosis. The last column gives the mean estimated volume of necrosis, V = L x T x D x 0.52. (The constant 0.52=\(\pi+6\)). The individual measurements are given in the appendix (page 208).

<table>
<thead>
<tr>
<th>Fibre-tip, and Laser power</th>
<th>Size of necrosis L (mm)</th>
<th>Size of necrosis T (mm)</th>
<th>Size of necrosis D (mm)</th>
<th>Volume of necrosis V (mm(^3))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bare fibre, 2W</td>
<td>16.5</td>
<td>17.5</td>
<td>14.5</td>
<td>2270</td>
</tr>
<tr>
<td>Metal needle, 2W</td>
<td>20.0</td>
<td>12.5</td>
<td>8.5</td>
<td>1134</td>
</tr>
<tr>
<td>Bare fibre, 4W</td>
<td>18.7</td>
<td>16.7</td>
<td>15.0</td>
<td>2494</td>
</tr>
<tr>
<td>Metal needle, 4W</td>
<td>28.3</td>
<td>12.7</td>
<td>11.3</td>
<td>2167</td>
</tr>
</tbody>
</table>
Figure 4.10: Sections of pig liver after ILP (805nm diode laser) using a bare fibre-tip, showing the typical necrotic lesions produced by using 2W (above) and 4W (below). A constant energy of 1000J was used. The necrosis has a well-defined haemorrhagic margin, and a cylindrical charred centre. The 4W lesion is slightly longer and has more central charring.

Figure 4.11: Sections of pig liver after ILP using a metal needle-tip, and 2W for 500s (above) or 4W for 250s (below). These necrotic lesions are longer but thinner than the ones produced by a bare fibre, and the 4W lesion is longer than the 2W one.
Figure 4.12: Sections of pig liver after ILP at 2W (1000J) using a metal needle (above) and bare fibre (below). Patent blood vessels (arrowed) can be seen adjacent to the relatively small necrotic areas.

Figure 4.13: Sections of pig liver after ILP, taken about 5mm away from the edge of the main necrotic zones. Above (2W, bare fibre), there is perivascular necrosis around a small thrombosed blood vessel. Below (4W, metal needle), 2 larger vessels are also thrombosed but have much less perivascular necrosis (arrows).
In the second pig experiment, using 4000J, there was considerable variability in the results. At 4W and 1000s, the needle-tip was blackened along 35mm, the distal 5mm being clean (fibre-tip was 1cm proximal to needle-tip), and more proximally the needle was slightly discoloured (Figure 4.14a); since the blackening extended to the entry point of the needle into the liver, the 2 subsequent 4W lesions were produced after inserting the needle 6cm into the liver (fibre-tip still 1cm proximal to needle-tip). In one of these cases the needle was blackened along 38mm, and in the other 48mm but with a clean 7mm segment in this latter blackened segment (Figure 4.15a); in both cases, the distal 5mm of needle-tip was also clean. The other main feature at these higher energies was that the fibre cladding within the needle was burnt back up the fibre 55mm (Figure 4.14a), 20mm and 50mm, respectively. In the first and last case, the liver tissue and metal needle, at the needle entry point, were seen to be visibly heating after 400s and 900s, respectively. The subsequent necrotic lesions produced were morphologically very irregular. What appeared to be happening was that a well-defined ellipsoidal zone of necrosis was initially developing, then, after a certain time (<400s in one case, and <900s in the other), the cladding of the fibre began to burn within the needle and rapidly back-track up the fibre with heating of the needle along its track, and subsequent proximal extension of the necrotic zone (Figure 4.14b). Figure 4.15b shows the necrosis from the needle which had a clean gap in the blackening - it can be seen that a large vessel splits the necrosis into 2 separate lesions; presumably the needle passed through the vessel, the flowing blood keeping this part of the needle and perivascular tissue free of thermal damage. The other main reason for the irregular morphology of the necrotic lesions was the phenomenon of perivascular necrosis around the smaller blood vessels traversing the necrosis (Figure 4.13) - this was seen in all 3 lesions produced at 4W and 4000J.

At 8W and 4000J, with the metal needle, the effects were more dramatic, and the necrotic lesions more irregular. The variation of the placement of the fibre-tip at 3cm, 2cm, and 1cm from the needle-tip showed that the distal limit of needle blackening was only 5mm away from the site of the fibre-tip, indicating that the heat propagated back up the needle rather than forwards. With the first lesion (fibre-tip 3cm from needle-tip, and 6cm of needle within liver), thermal changes were seen at the needle entry point after only 100s; by 400s the heat had propagated 50mm back up the needle (from its entry point into the liver), and since the needle was white-hot proximally, the treatment was stopped. The fibre was found to have snapped 60mm from its tip. With the second lesion, the needle and fibre-tip were deeper in the liver, and thermal effects were seen at the needle entry point after 430s - 45mm of needle was blackened, and 40mm of the fibre cladding burnt back. The third lesion at 8W showed 50mm of needle blackening, and again 40mm of fibre cladding burnt; in this case the fibre-tip was 1cm proximal to the needle-tip which was 7cm into the liver - no thermal effects at the entry point were seen. The volumes of the necrotic lesions could not be estimated because of their very irregular and unpredictable nature.
Figure 4.14: (a) Metal needle (above) and bare fibre (below) after ILP in second pig, using 4W and 1000s; the needle was inserted 4cm into the liver, and tissue changes were seen at the entry point of the needle during ILP. Blackening of the metal needle extends 5mm from the needle-tip to the flag, with some discolouration more proximally. The cladding of the optical fibre is seen to be burnt for 55mm from the tip.
(b) Corresponding necrotic lesion, extending to liver capsule. Central linear charring is present in the left side of the necrotic lesion, although this did not extend along the necrosis, towards the liver capsule. The point at which the needle was inserted into the liver is marked by a suture (arrow).
Figure 4.15: (a) Metal needle after inserting 6cm into the pig liver, the fibre-tip 1cm proximal to the needle-tip, and the laser activated at 4W for 1000s (4000J). The needle is blackened along a 48mm segment, within which 7mm is clean (arrow). (b) Corresponding section of liver showing a discontinuous necrotic lesion which is separated by a vessel (arrow) not showing any evidence of thrombosis.
The single bare fibre lesion in the liver at 8W had been produced with the fibre inserted 3.5cm into the liver tissue. This produced a more uniform necrotic lesion of 40 x 20 x 20mm (estimated volume, 8320mm³); however, the cladding had burnt back to the entry point of the fibre, and the fibre fractured during withdrawal, leaving the broken segment of fibre in situ. On sectioning the liver, it was also noted that the fibre was broken in several places in the centre of the necrotic lesion. Furthermore, the necrosis had extended back up to the liver capsule.

4.4. DISCUSSION

4.4.1. RAT LIVER MODEL FOR ILP

In the majority of the experiments the model used for in vivo ILP was a lobe of rat liver. This has a diameter of 25-30mm, and there are many advantages in using it for ILP: rats are readily available and easy to manage; the liver lobe can be easily accessed by laparotomy for in vivo ILP; the liver lobe has a fairly consistent shape and size; accurate localisation of the fibre-tip is possible; some of the effects of ILP (such as loss of aiming beam and surface effects can be directly observed; there are no large blood vessels to cause a marked reduction in the size of necrosis, eg. if the fibre-tip lies adjacent to such a vessel.

Some of the disadvantages of using the rat liver for ILP are: the extension of the necrosis to the superior and inferior surfaces of the liver lobe means that some heat is lost to the atmosphere; the size of necrosis is likely to be greater than one would expect in a larger liver where the necrotic lesion would be completely surrounded by liver, hence the rat liver model is more useful for comparative work rather than an indicator of the size of necrosis expected in humans from the parameters used; the small size of the rat liver lobe means that there is a limit to the size of necrosis which can be evaluated; the size of the lobe may influence the size of necrosis itself, possibly by limiting the extent of thermal damage; edge effects (wedge necrosis) may make reliable measurement of necrosis difficult.

Biological variability is inevitable in any in vivo experiments. Other factors causing variable necrosis during ILP despite using the same parameters include fibre-tip deterioration, changing optical and thermal properties of tissue as it is coagulated, and variable cooling by flowing blood in any adjacent vessels. This latter factor is likely to cause greater variation in larger animal models.

Overall, the rat liver served as a very useful model for the experiments that were performed, and allowed practically relevant differences in laser parameters to be relatively easily detected.
4.4.2. SIGNIFICANCE OF CHARRING DURING ILP

The strong association between the extent of tissue charring around the fibre-tip and the size of necrosis was a new finding of major importance. Lesions which showed no or minimal central charring, had a much smaller diameter of coagulative necrosis than those in which greater charring was present. The early loss of the He-Ne aiming beam was consistently predictive of tissue charring and greater necrosis than if the aiming beam was visible throughout ILP. It would be reasonable to assume that the loss of the aiming beam is associated with decreased penetration of the laser light. Hence, it can be inferred that decreased tissue penetration of the laser light results in a greater volume of thermal damage than increased penetration, contrary to what was previously thought.

It is probable that once charring is initiated, the laser light is strongly absorbed by the black char, with a subsequent large temperature rise around the immediate vicinity of the fibre-tip, and further char formation. The fibre-tip would then act as a point heat source rather than a distributed heat source (or a point optical source, as would be the case with deeper tissue penetration of laser light). Tissue heating and consequent necrosis then occurs as a result of thermal conduction, and the extent of thermal damage depends on the temperature gradients achieved as well as the length of time the tissue is exposed to the elevated temperatures (Thomsen, 1991).

Charring around the fibre-tip may weaken the tip itself. However, at powers of 1-4W in rat or pig liver, there were no cases of the tip breaking and a fragment remaining behind, even though there was sometimes resistance to withdrawing the fibre because of sticking to the tissue char. If a fragment is left behind then this would be rendered sterile in view of the high temperatures achieved during ILP (in the presence of charring these could theoretically be as high as 300-400°C). The fibre-tip did break with some fragments left behind when using the higher power of 8W in the pig experiment.

At the same time as this in vivo study was being conducted, Wyman et al (1992a) published some in vitro work, in which they found greater thermal damage during ILP if a small amount of tissue debris was attached to the fibre-tip prior to activating the laser; they also found an association between tissue charring and necrosis size.

The in vivo data presented in this thesis shows that the mechanism of action of ILP during the production of clinically useful necrosis is completely opposite to what was originally proposed. It has always been felt that charring should be avoided during ILP, the argument being that it reduces the extent of thermal damage by reducing the penetration depth of the laser light. However, it is now clear that the less the light penetrates and the more focused its absorption, the higher the local temperature rise and the greater the extent of thermal damage. In the examples of no charring and ILP performed with deep
penetration of laser light (even at 3W using the 1064nm Nd:YAG laser), the necrosis produced is consistently much less than when charring occurs.

4.4.3. FACTORS WHICH CAUSE CHARRING

The crucial factor which causes charring of tissue around the optical fibre-tip is the temperature achieved. This is determined by the optical fibre-tip, laser wavelength used, the power and exposure time, as well as the optical and thermal properties of the tissue; the last of these has been kept constant during the experiments. An unpredictable factor is the inadvertent insertion of the fibre-tip into or close to a large blood vessel, the flowing blood in which will tend to lower the peak temperature achieved during ILP.

4.4.3.1. Fibre-tip: cladding material

The type of material of which the cladding of an optical fibre is made has been shown to be of considerable relevance. This has not previously been noted and most groups don't report the type of fibre they are using for ILP, nor mention whether the cladding has been removed.

ILP using a plastic clad fibre with its cladding intact inevitably results in burning of the cladding - this probably initiates charring leading on to the chain of events described above. ILP with a silica clad fibre (and a 1064nm Nd:YAG laser) resulted in less charring, probably because the silica cladding is much more resilient to temperature rises and does not burn easily. As a result the plastic clad fibres gave much larger necrotic lesions than the silica clad ones. Removing the cladding from plastic clad fibres did not negate this difference. This is likely to be related to the difficulty in completely removing the plastic cladding by mechanical methods. It is probable that even a small amount of debris on the fibre-tip is sufficient to initiate the cycle of burning and charring. The 0.2mm plastic fibre charred more and gave larger necrotic lesions than the 0.4mm fibre at 200J, and this may be related to the greater difficulty of removing the cladding from the smaller fibre, thus providing more debris for burning; this difference was not apparent at the higher energy. The other explanation is that the smaller fibre has a decreased surface area, and therefore a higher power density at its tip, and so charring is more likely to be initiated earlier and at lower energies.

This data suggests that to achieve greater necrosis using a 1064nm Nd:YAG laser, a plastic clad fibre should be used, at a power of 2W and energy of 1000J. The cladding is preferably left intact to ensure that there is something to burn and initiate char formation. It is preferable to remove the buffer coat/jacket, since this reveals a previously unexposed part of the fibre which is easier to sterilise. Damaging the cladding while removing the buffer coat/jacket is of no consequence for ILP.
4.4.3.2. Laser wavelength

The 1064nm Nd:YAG laser wavelength was originally proposed to be the most suitable wavelength for ILP because of its relatively deep tissue penetration; this theoretical assumption has never been questioned or tested in practice until now. The data presented in this thesis shows clearly that less penetrating wavelengths (1320nm, 805nm, and 488/514nm) do in fact cause greater thermal damage during ILP than 1064nm.

The absorption coefficient of the 1320nm Nd:YAG wavelength is ten times greater than the 1064nm wavelength in water and saline (Stokes et al, 1981), and it has been shown to be highly absorbed in brain tissue (Mordon et al, 1990). The 805nm diode wavelength is also more heavily absorbed in soft tissue compared to the 1064nm Nd:YAG wavelength (Jacques et al, 1992), especially in the presence of blood (Shen et al, 1993), as is the 488/514nm wavelength. The data presented in this thesis has demonstrated that during ILP the 1320nm, 805nm and 488/514nm wavelengths cause charring in liver tissue relatively quickly and at lower powers, compared to the 1064nm wavelength. This is likely to be due to the laser energy being deposited in a much smaller tissue volume around the fibre-tip, resulting in higher temperatures (Svaasand et al, 1990), and early initiation of charring.

4.4.3.3. Laser power and energy

The power at which charring occurs is dependent on the exposure time, wavelength and type of fibre-tip used. A 1064nm Nd:YAG laser will only rarely cause charring (at powers of 1-3W) when a silica clad fibre is used; with a plastic clad fibre charring occurs consistently at a power of 2W and energy of 1000J, but only sometimes with an energy of 200J. The 1320nm Nd:YAG laser produces only a small amount of charring at 1W, but at 2W and 3W this is much more marked. The 805nm diode laser and the 488nm/514nm Argon lasers consistently produce marked charring at 1W, the laser energy being confined to a much smaller depth with subsequent greater rise in tissue temperature even at 1W.

4.4.4. ROLE OF PRE-CHARRED FIBRE-TIPS

Pre-charring the bare optical fibre-tip using the 1064nm Nd:YAG laser allows the cycle of reduced light penetration, higher local temperatures and more charring to be initiated, with a subsequent consistent and dramatic increase in the size of necrosis, compared to a clean fibre-tip at the same wavelength. Pre-charring at the 1320nm wavelength makes little difference to the extent of necrosis, since the charring cycle begins spontaneously even with a clean fibre-tip. With the tips pre-charred, the size of necrosis obtained by the 1064nm and 1320nm wavelengths was essentially the same at a power of 3W, although at 1W and 2W there was a difference between the two; this cannot be simply explained, since at 1W the 1064nm laser gave larger lesions, but at 2W the 1320nm laser gave larger lesions. This difference may be related to the amount of char present on the pre-charred...
fibre-tip at the onset of ILP (which was variable), and it may be that if there had been a larger number of lesions from which to calculate the means (ie. more than three) there would be no difference at 1W and 2W.

Thus, at present, this data does not conclusively show that in the presence of charring the size of necrosis is independent of the laser wavelength used. This has, however, been shown to be the case by others during non-interstitial contact laser irradiation, in vitro (Shen et al, 1993).

Pre-charring bare optical fibres is likely only to be beneficial when using the 1064nm Nd:YAG laser with silica or hard polymer clad fibres. Although plastic clad fibres can give similar necrotic lesions with the 1064nm Nd:YAG laser without the need for pre-charring, silica clad and hard polymer fibres do offer the advantage of being more resilient than the plastic clad fibres.

**4.4.5. OPTIMAL LASER WAVELENGTH FOR ILP**

Using similar fibre-tips (silica or hard polymer clad), it is clear that the 1064nm wavelength produces less necrosis than 1320nm, 805nm, or 488nm/514nm wavelengths at given powers. The last of these is the Argon laser, which is unsuitable for ILP because, at a power of 2W, there is too rapid a build-up of energy leading to mini-explosions and unpredictable forward channelling (creating a tunnel) of the light beam. A power of 1W with the Argon laser appears safe for ILP, but the necrotic lesions are smaller than those created by the other wavelengths (1320nm and 805nm) at 2W and 3W, and the exposure time of 1000s is relatively long.

There is little difference between the 1320nm and 805nm wavelengths with respect to the final size of necrosis. However, a more controlled tissue destruction was achieved with the 1320nm wavelength in rat liver, with less dramatic surface effects. Although in rat liver, mini-explosions were heard with the 805nm wavelength at 2W and 3W, and the liver surface ruptured on two occasions at 3W, this was not found to be a problem in pig liver, where the 805nm laser was found to safely induce necrosis at powers of 2-4W.

The 805nm laser is a new high power semiconductor laser which has many potential advantages - it is simple to use, does not require water cooling or three-phase electrical power, and is small, compact and portable (Manni, 1992; Wyman et al, 1992). This makes it more acceptable to clinicians and very suitable for use in different imaging suites, since ILP is an image-guided technique.

At present, the 1064nm Nd:YAG laser is the most widely installed laser. Therefore, initially, the most practical option is to use pre-charred fibre-tips or plastic clad fibres with
this laser for ILP. The future is likely to lie in the wider availability of cheaper high power diode lasers, in which case the type of bare optical fibre used will become irrelevant.

4.4.6. OPTIMAL POWER FOR ILP

A power of 2W was initially used in the fibre-tip experiments, since this is what can currently be delivered clinically down each fibre of a 1x4 coupler (Amin et al, 1993a). Previous experimental work has shown that the optimal energy to deliver down each fibre of a coupler is 1000J (Steger et al, 1992). This was the energy used for most of the necrotic lesions, and the power varied in the later experiments. Lower energies (200J) were used in the fibre-tip experiments to evaluate whether charring occurs at these energies.

In rat liver, larger necrotic lesions were generally found at powers of 2W and 3W than at 1W, using a constant energy of 1000J. This is likely to be due to the slower rate of energy deposition at this lower power resulting in early thermal equilibrium, a lower maximum fibre-tip temperature, and a smaller volume in which the tissue temperature is high enough for long enough to cause necrosis. The plateau observed at 2-3W may represent the maximum size of necrosis attainable at the energy used (1000J), but it may also be related to the size limitation of the rat liver model, with necrotic lesions greater than 20mm often partly extending to the edge of the liver lobe. If this plateau is real, it needs to be confirmed in a larger animal model and then applied clinically, since a power of 3W offers the advantage of a shorter exposure time (and so a shorter total treatment time) to deliver 1000J of energy compared to a power of 2W.

Although the charring, when present, was cylindrical at 2W and 3W, the dimensions of the necrosis remained symmetrical with the transverse widths of necrosis being similar to the longitudinal lengths at the wavelengths and powers used, except at 2W with the Argon laser. This may be explained by the relatively slow forward propagation of the char (and laser light beam) from the Nd:YAG and diode lasers during ILP in rat liver - this allows time for the heat to be conducted laterally thereby sufficiently increasing the transverse width of necrosis; the longitudinal length of necrosis increases gradually by the forward tunnelling of the laser beam. Hence, the charring (immediately around the path of the laser beam, where temperatures are highest) appears cylindrical, whereas the necrosis is roughly circular. However, with the Argon laser at 2W, the energy deposition is too fast and the forward propagation of the char (and laser light beam) too rapid to allow sufficient time for maximal lateral (or transverse) necrosis to occur. Therefore, in this case, cylindrical charring is associated with an ellipsoidal necrosis with a greater longitudinal length than transverse width of necrosis.
Evaluation of the 805nm laser in pig liver showed fairly spherical necrotic lesions to be safely produced at powers of 2W and 4W (1000J), using a bare fibre-tip. As expected the necrotic lesions were slightly smaller in pig liver, compared to rat liver. Interestingly, the dimensions and volumes of necrosis at 2W and 4W in pig liver were similar, indicating that it may be possible to use 4W for only 250s clinically, reducing treatment times further. However, the absence of forward tunnelling and ellipsoidal lesions may have been due to the fact that the hard polymer clad fibres used for these experiments had their cladding burnt back up the fibre - this directs the thermal damage backwards.

The data does suggest that powers greater than 2W (3W or 4W) may be potentially useful for ILP and allow shorter treatment times (at the same energy). Other groups have found ellipsoidal lesions at powers of 3W or above, and preliminary in vitro work, using 4W from a 1064nm Nd:YAG laser, showed extensive forward tunnelling of the char and necrosis (longitudinal x transverse lengths of necrosis = 45x11mm). This is the main potential danger of using high powers and silica clad bare fibre-tips during ILP. It should also be remembered that the main limiting factor to using powers above 2W is the ability of the coupling system in the beam-splitter to tolerate higher powers; at present, more than 2W per fibre is likely to cause overheating and damage to the coupler.

4.4.7. POTENTIAL OF METAL NEEDLE-TIPS

In the first series of experiments, focusing all of the laser energy (at 1064nm) into a 5mm segment of a steel needle clearly produced much greater necrosis compared to a bare silica clad fibre during ILP in rat liver. Compared to the effects from an 805nm diode laser, the needle-tip produced larger necrotic lesions at 1W (mean transverse widths, 10.3 vs 15.7, respectively), with little difference at 2W, and at 3W the transverse widths of the necrotic lesions were slightly less with the needle-tip (means, 21.0 vs 17.3, respectively). The most likely explanation for these findings is that at 1W charring occurs less rapidly around the bare fibre-tip, with less focusing of energy than the needle-tip; at 2W charring rapidly occurs, and so the energy is quickly focused around the bare-tip; at 3W, the loss of heat in smoke by the metal-tip meant less energy was available to increase the size of necrosis. A plateau effect between 2W and 3W may be due to the same reason, although it may be that increasing the power above 2W while keeping the energy constant, does not affect the size of necrosis. Attaching a needle-tip to an optical fibre by "crimping" is unacceptable clinically because of the very high risk of the needle segment being retained in situ, stuck to the charred tissue.

In the pig experiments with the metal needle, the objective was to see if the length of the necrotic lesions could be safely increased, as well as the breadth by using higher powers, and to compare these lesions with those produced from a bare fibre-tip and a more heavily absorbed 805nm wavelength. Table 4.9 shows that at 1000J, although longer lesions
were produced with the metal needles, they were narrower and of smaller volume than the bare fibre-tip lesions. The main reason for this is that with the energy distributed over a longer length (with the metal needle) the temperature rise at any point will be less; the surrounding blood flow results in more cooling and subsequently smaller thermal gradients compared to a bare fibre-tip. In the latter case, the energy from an 805nm laser is highly focused around the fibre-tip because of the rapid formation of char, large thermal gradients are created and a relatively larger spherical necrotic lesion develops. With the metal needle work, some energy is also taken up with heating the needle and burning the cladding, which would also result in smaller volume necrosis; this is likely to be a relatively small effect.

At higher energies (4000J), the necrotic lesions were uncontrolled and unpredictable with the metal needle, the main cause of this being the fibre cladding burning back within the needle, the light then leaking from the sides of the fibre, resulting in further burning of cladding - the heat was therefore being propagated back up the fibre in a variable fashion. With the bare fibre at 8W, a fairly uniform, large volume necrotic lesion was produced, but the cladding was again burnt back up to the liver capsule. The fibre used had hard polymer cladding which is more prone to burning at high temperatures than a silica clad fibre. The latter, therefore needs to be evaluated in a similar study, but the buffer coat/jacket should be removed over a long length since this may also burn. A further simple experiment was performed in air, comparing the silica clad and polymer clad fibre; the fibre-tip was placed in the centre of a 19 gauge steel needle, and the laser (805nm) activated at 8W. The surface of the needle could be seen to be heating, and as expected with the polymer clad fibre, the heat rapidly propagated back up towards the hub of the needle, and on withdrawing the fibre the cladding was heavily burnt. With the silica clad fibre, heat was seen to propagate equally forwards and backwards, the total length of heated needle being 26mm, remaining like this from 20s to 200s - the tip of the fibre was only slightly damaged. This shows that silica clad fibres may give a more predictable necrosis when used inside metal needles for ILP, although steel needles may not be ideal since one would expect significantly less conduction of heat along the needle in vivo, and so the subsequent necrosis may not differ much from a bare silica clad fibre. Therefore, needles with greater thermal conductivity than steel (eg. copper) should also be evaluated, to try to get longer, broader necrosis at high laser powers.

A significant problem with using metal needles is the risk of them sticking firmly to charred tissue - this was a persistent problem with the rat liver ILP work, and to avoid this in the pig, the needles were frequently rotated. Inadvertent failure to rotate can result in considerable charred tissue debris remaining stuck to the needle on withdrawing at the end of the procedure - this can consequently give rise to a large channel being created and increase the risk of haemorrhage. Use of non-stick metals may help to overcome this problem.
This data has demonstrated that the principle of performing ILP by focusing all of the laser energy into a segment of metal needle can give greater thermal damage than a bare fibre alone, when using a Nd:YAG laser. In theory, higher powers can be used down metal needles to increase the length and breadth of necrosis in a more controlled manner than with bare fibre-tips, but technical problems exist; these need to be addressed by evaluating the role of silica clad fibres and different types of metal needles.

4.4.8. PERIVASCULAR NECROSIS - AN IMPORTANT NEW FINDING

Sparing of large blood vessels and tissue around them (due to cooling by flowing blood) has previously been described, but the perivascular necrosis and thrombosis of adjacent small vessels traversing the main necrotic lesion has not been noted in other studies using powers of 1-4W in pig and dog liver. A study using much higher powers of 80W over 10s for ILP in pig liver does mention thrombosis of adjacent blood vessels with necrosis of their walls and perivascular oedema (Godlewski et al, 1988a). Our findings were more marked and are likely to be due to escape of steam bubbles away from the heated zone via these vessels (Amin et al, 1993a) - this has little effect on large blood vessels (Figure 4.12), but smaller vessels have low blood flow and it is likely that the heat from the steam is deposited in their walls; the slower the blood flow (in the smallest vessels), the greater the heat deposition (Figure 4.13). This finding has potentially useful clinical implications in that the vascular thrombosis may prevent haematogenous tumour cell dissemination (Overgaard, 1977).

4.4.9. CONCLUSIONS

These experimental findings have changed our thinking of the mechanism of action of ILP and provided the basis to optimise and improve the technique of ILP.

The presence of charring was previously thought to be undesirable during ILP, but the data presented in this chapter has clearly shown that charring is not only advantageous, but is an essential requirement if adequate thermal damage is to be produced.

The type of optical fibre used for ILP was thought not to be relevant, but it is now apparent that when using a 1064nm Nd:YAG laser, plastic clad fibres or pre-charred silica/hard polymer clad fibres produce much greater thermal damage than clean silica or hard polymer clad fibres.

The widespread belief that the 1064nm Nd:YAG laser was most suitable for ILP has also been shown to be wrong: less penetrating wavelengths cause charring and greater necrosis. The 1320nm Nd:YAG, 805nm diode and 488nm/514nm Argon lasers have been used for ILP for the first time. The 805nm diode laser is a new semiconductor laser
with many advantages over other lasers, and it produces the largest necrotic lesions during ILP. This is the laser of the future, and with the development of a reliable beam-splitting device, it is likely to become the laser of choice for ILP.

The concept of the optical fibre-tip acting as a point heat source during ILP, with maximum tissue damage occurring by thermal conduction rather than optical penetration, can be extended by using metal-tipped fibres. The work reported in this chapter has been only a preliminary evaluation and needs to be taken further using different metals and fibres.

However, with this hot-tip concept, one must look critically at the value of using lasers to produce such thermal damage, and alternative cheaper hot-tip modalities need to be evaluated and compared with lasers for interstitial thermal therapy. Lasers do have the advantage of being able to deliver precise quantities of energy down thin flexible optical fibres - these fibres can easily be passed down needles less than 1mm in outer diameter, and this makes most deep-seated tumours accessible to ILP, if appropriate. Where a laser is already installed, it is relatively simple and cheap to extend its application to ILP. A promising new percutaneous method for interstitial thermal destruction of liver tumours is RF electrocautery (see section 1.3.4.4); necrotic lesions measuring 1x2cm have been safely produced in pig liver via a hot tip which is attached to a needle 1.1mm in diameter. This technique needs to be compared with ILP, with respect to practicality, safety and costs.

ILP is still in the early stages of evolution, and the optimal parameters for ILP need to be continually evaluated and redefined, and the technique optimised as new findings of importance become known.
CHAPTER 5: ASSESSMENT OF EXTENT OF NECROSIS FOLLOWING ILP

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5.2. CT-pathologic correlation of ILP-induced necrosis
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5.1. HISTOPATHOLOGICAL AND HISTOCHEMICAL EVALUATION OF ILP-INDUCED NECROSIS

5.1.1. INTRODUCTION

A reliable way of evaluating the effects of ILP is needed. Imaging can non-invasively give a guide to the extent of thermal destruction, which may be seen on dynamic contrast enhanced CT scans as a new area of non-enhancement 24hrs after ILP (Amin et al, 1993a). Ideally however, careful histological assessment of the treated tumour should also be undertaken, by performing core biopsies. Therefore, it is essential that the histological features following ILP are well understood.

Cells which have been destroyed by ILP may appear to be viable on standard histological assessment if they look morphologically intact. A more sensitive way of detecting cell viability is by histochemical analysis. Demonstration of the presence of the mitochondrial enzyme, diaphorase, can indicate cell viability (Bancroft, 1975; Pearse, 1972); it is rapidly denatured by heat, and its activity subsides immediately after cell death. By this method, the border between stained (black or purple) normal and unstained devitalised structures is delineated sharply, permitting an accurate determination of the extent of necrotic tissue.

In chapter 4, the importance of charring during ILP was highlighted. When charring does occur, the subsequent tissue necrosis is due to thermal conduction from a very hot point source, since all of the laser energy is focused into the char; in the absence of charring, the laser light is scattered and penetrates the tissue around the fibre-tip, thermal damage occurring as a result of subsequent absorption of the light by tissue, as heat (Amin et al, 1993b; Wyman et al, 1992a). In chapter 4 it was shown that charring consistently occurs when using 0.2mm plastic clad optical fibres, but does not occur with 0.4mm silica clad fibres, at a power of 2W and exposure time of 500s (Amin et al, 1993c).

The aims of this study were: (a) To describe the histological features of charred and uncharred necrotic lesions in rat liver, following ILP, in order to ascertain whether there is any significant difference between the two, (b) To determine the extent of thermal damage after ILP, using histochemical analysis as well as routine haematoxylin and eosin (H & E) staining, and (c) To evaluate the temporal changes in the histological features of the necrosis, immediately after ILP and up to 3 weeks later.

5.1.2. METHODS

5.1.2.1. ILP technique
Twenty four Wistar rats (weight 250-300g) had ILP performed as described in section 4.2.1. An optical fibre was plane-cleaved and its distal 3mm of buffer coat and/or jacket
stripped, leaving the cladding intact around the core of the fibre-tip. A power output of 2W or 3W was selected from a Nd:YAG (1064nm) laser. Approximately 1cm of the fibre-tip was then inserted into the rat liver, and the laser activated for an exposure time of 200-500s.

After ILP, the fibre was removed, the liver lobe replaced into the abdomen, the wound closed, and the rats allowed to fully recover, except in 2 cases when the rats were killed immediately after ILP.

5.1.2.2. Histological comparison of charred and uncharred lesions at 24hrs
In 5 rats a 0.2mm plastic clad optical fibre was used in order to achieve a necrotic lesion with central charring; in another 5 rats a 0.4mm silica clad fibre was used to obtain necrosis without charring, at powers of 2W for 500s (Amin et al, 1993c). These 10 rats were sacrificed 24hrs after ILP, by carbon dioxide inhalation, and the treated lobes of liver immediately resected. The zone of coagulative necrosis was clearly seen on the liver surface as a well-defined yellow circular area (see Figure 4.4). A block measuring approximately 4mm thick was taken from each side of the centre of the necrotic lesion, in a plane perpendicular to the track of the fibre; this block included the lesion and surrounding hepatic tissue. One block was placed in 10% buffered formalin, fixed at 4°C for 2 days, then embedded in paraffin wax and cut into 4 micrometer sections, followed by staining with haematoxylin and eosin (H & E). The other block was snap frozen (within 1 hour of killing the rat) using liquid nitrogen and cryostat sections were cut. Staining was performed with H & E, and for nicotinamide adenine dinucleotide phosphate (NADPH) diaphorase enzyme (on separate sections), the latter by using the redox indicator nitro blue tetrazolium chloride, which is reduced by NADPH diaphorase (Bancroft, 1975).

5.1.2.3. Temporal assessment of ILP-induced necrosis
The remaining 14 rats had ILP performed with a 0.2mm plastic clad fibre. The power used was 2-3W for an exposure time of 200-500s. The objective here was to achieve a necrotic lesion of approximately 1cm in diameter, and this was estimated from the surface effects. The presence of charring was not a concern, since this part of the study was looking at the overall morphology of the lesion outside the central zones (which were the only zones which were different between charred and uncharred lesions, see section 5.1.3.1). These 14 rats were sacrificed at various times after ILP, as follows: two immediately after ILP; three at 24hrs; three at 3 days; three at 10 days; three at 3 weeks. The liver lobes were resected and stained with H & E and for diaphorase as described above.

5.1.2.4. Statistical analysis
The mean transverse width (perpendicular to the fibre track) of necrosis was calculated for the charred and uncharred lesions, and compared using Wilcoxon rank sum test for two independent samples.
5.1.3. RESULTS

The typical appearance of the necrotic lesion on the surface of the resected liver lobe is shown in Figure 4.4.

All of the lesions produced by the 0.2mm plastic clad fibre had central charring surrounded by coagulative necrosis, whereas those produced by the 0.4mm silica clad fibre did not show any central charring (see Figure 4.5). Macroscopically, the charred lesions had a small area of central cavitation 1-2mm in diameter. Around this was a layer of blackened charred tissue, surrounded by a zone of yellow coagulative necrosis, with a well-defined outer margin; the more central part of this necrosis was slightly discoloured (red/brown). Uncharred lesions were well-defined, homogenous zones of yellow coagulative necrosis.

The mean transverse width of the charred lesions was 19mm (range 15-22mm), compared with a mean of 8mm (range 5-12mm) of the uncharred lesions (p<0.01). The respective mean width of the charring was 3mm (range 2-4mm) and 0mm. The individual results are given in the appendix (page 209).

5.1.3.1. Uncharred versus charred lesions at 24hrs

Microscopic examination of the charred lesions revealed a targetoid appearance with six distinct concentric zones: Zone 1 - central zone of cavitation (1-3mm), incompletely filled by red cells and amorphous pink material; zone 2 - charred zone, containing a thin irregular band of black/brown charred tissue; zone 3 - "condensed zone", with structureless densely eosinophilic background material and pyknotic elongated nuclei (zones 2 and 3 were 1-2mm thick); zone 4 - "preserved zone", consisting of a broader zone in which the structure of the liver, including fine nuclear detail was well preserved apart from some mild cytoplasmic pallor and fine vacuolation (this measured 2-6mm); zone 5 - "pallid necrosis", showing increased cytoplasmic pallor and vacuolation, some loss of nuclei and focal cell dissociation, (measuring 1-7mm); zone 6 - "active necrosis", containing a sharp band of neutrophils, outside which was a band of necrotic hepatocytes with cytoplasmic eosinophilia, variable loss of nuclei, and a neutrophilic infiltrate of the sinusoids which also contained apoptotic fragments (zone 6 measured 1-4 mm). There was then a sharp smooth boundary with adjacent normal liver, which displayed minimal changes (slight increase in periportal mononuclear cells).

Microscopic examination of the uncharred lesions showed no central cavitation, charring or "condensed" tissue, ie. complete absence of zones 1, 2 and 3 described above. Instead there was a broad central zone of homogeneous "preserved" hepatocytes, followed by peripheral zones of "pallid necrosis" and "active necrosis" (similar to zones 4, 5 and 6 above). The zone proportions were similar for the charred and uncharred lesions. Figures 5.1 and 5.2 show the main histological features of charred and uncharred lesions.
Similar vascular changes were seen in both charred and uncharred lesions. Occlusive thrombus was seen in smaller vessels, and larger vessels had focal detachment of their endothelium, predominantly in zones 5 and 6. In the periphery, the larger vessels also had shadows of viable tissue behind them, probably due to a "heat-sink" effect of flowing blood.

Histochemical analysis using diaphorase staining showed similar features in the charred and uncharred necrotic lesions. There was strong diaphorase positivity of normal hepatocytes surrounding the necrosis, and complete absence of staining of the necrosis itself (zones 1-6). There was a strikingly abrupt transition between stained and unstained tissue, which corresponded exactly with the junction between viable hepatocytes and "active necrosis" (zone 6) noted on the routine H & E staining. Figure 5.3(a) shows a necrotic lesion after staining with diaphorase.

5.1.3.2. Temporal changes
H & E stained sections taken from the livers immediately after treatment showed central cavitation, charring and condensed zones (zones 1, 2 and 3) in one case, but peripherally there was remarkably little morphological change; the other liver examined immediately after ILP showed patchy congestion only on H & E staining. It was not possible to see the viable/non-viable border of these lesions (Figure 5.4(a)). The diaphorase staining, however, showed an unequivocal abrupt transition from negative to positive staining at a similar distance from the centre of the necrosis as in the 24hr lesions (Figure 5.4(b)). The lesions from days 1, 3, 10, and 21 showed a progression of changes associated with repair (Figure 5.5). The central cavitation, charring, "condensed" and "preserved" zones (zones 1-4) remained unchanged in appearance with no cellular ingress. The zone of "active necrosis" (zone 6) became broader and developed into granulation tissue, which by day 21 had matured into young fibrous tissue, encapsulating the necrosis. The band of neutrophils at the junction between zones 6 and 5 remained sharp though diminishing in intensity in later lesions. There was never any ingress of neutrophils into the inner 5 zones observed in any of the lesions. In 3 out of the 6 later lesions (days 10 and 21) there was no cellular ingress into these zones. In the remaining 3 late lesions, however, occasional macrophages were seen in these zones, apparently originating from peripheral portal tracts radiating out into zone 5. These were seen on the diaphorase stain as positive cells in the non-viable zone (Figure 5.3(b) and (c)).

Diaphorase staining showed that the margin of viable hepatocytes remained sharp and constant throughout the time course. Within zone 6 ("active necrosis"), although the hepatocytes were non-viable, a blush of positivity developed which reflected the accumulation of macrophages, mast cells and other cells of granulation tissue (Figure 5.3).
Figure 5.1: Low power photomicrograph of a necrotic lesion 24hrs after ILP.
(a) Charred lesion. (b) Uncharred lesion. (Magnification x4, H & E stain).
Figure 5.2: High power of zones of necrosis (H & E).  (a) Zones 1-5 (numbered) (x100).  
(b) Zones 5 and 6; N represents normal liver (x100).  (c) Higher magnification of "preserved" zone 4, with preservation of nuclei and sinusoidal architecture, and some cytoplasmic vacuolation (x400).  (d) Junction of zones 4 and 5 at higher power (x400).
Figure 5.2 (continued)
Figure 5.3: (a) Diaphorase staining at 24hrs, with a sharp border between stained viable tissue and unstained non-viable tissue (x20). (b) At day 10, there is some cellular ingress into non-viable zone, seen as diaphorase positive cells (x40). (c) Higher magnification shows these cells are macrophages (arrows) (x400).
Figure 5.4: (a) Low power photomicrograph of rat liver immediately after ILP with H & E staining, showing patchy congestion only (x4). (b) Diaphorase staining immediately after ILP, with clear demarcation of viable and non-viable tissue.
Figure 5.5: Temporal changes after ILP. (a) Three days after ILP, there is a clear demarcation between necrosis and normal liver (N) (x20). (b) By day 10, there is a layer of granulation tissue (G) surrounded by fibrosis (F) outside zones 5 and 6 (x40). (c) At day 21, zones 1-5 are still seen, and zone 6 has been largely replaced by fibrosis (x40).
5.1.4. DISCUSSION

This study has confirmed that when using the same power/time combination to perform ILP in rat liver, the presence of charring is associated with significantly larger necrotic lesions than when charring is absent. The possible reasons for this phenomenon are discussed elsewhere in this thesis (see section 4.4.3).

We have also shown that, apart from central cavitation and a thin layer of charring and "condensed" tissue, the predominant histological features of ILP-induced necrosis are similar in the presence or absence of charring. Also, the boundaries of the ILP-induced lesions are similarly defined on H & E staining and histochemical enzyme analysis (using diaphorase) 24hrs or more after ILP. This is consistent with the findings of Castren-persons et al (1992) who used lactate dehydrogenase activity for their histochemical evaluation.

The main finding of interest was that of a broad zone of "preserved" hepatocytes (zone 4) within the necrotic lesion, present for at least 3 weeks, outside which (where the temperature is lower) was a zone of active necrosis. It is likely that zone 4 represents instantaneous heat fixation of the hepatocytes. The diaphorase staining technique clearly showed that the cells in zone 4 were not viable, even though they demonstrated only minimal morphological abnormalities on H & E staining. This is of importance because of the risk of misinterpreting needle biopsies from this zone (eg. after treating liver tumours) as indicating viable tissue if routine H & E staining is used alone. The other significant finding was the almost normal appearance on H & E of most of the lesion immediately after ILP with inability to define its margins, whereas the boundaries of the necrosis were clearly defined using histochemical staining for diaphorase. It is unlikely that the margins of necrosis, at times of 24hrs or more after ILP, extend beyond those defined by diaphorase staining immediately after ILP.

There are several groups performing experimental work on ILP, and a review of the pathological findings in normal liver after ILP has shown that there is general agreement on the following features (section 2.3.2.5): a central zone of cavitation and charring, surrounded by a broad zone of coagulative necrosis, and bounded by a transition zone of inflammatory cells. The central charring and micro-cavitation are due to the very high temperatures around the fibre-tip, tissue water boiling, and steam formation (Brackett et al, 1986). By 4-7 days, granulation tissue is apparent in the periphery of the lesion, with infiltration of neutrophils, giant cells and macrophages, and the appearance of proliferating bile ductules and neovascularisation. This is followed by the development of a fibrous capsule, and the necrotic tissue is replaced by phagocytosis, eventually only a small fibrous nodule remaining 3-8 weeks after ILP. The zone of coagulative necrosis comprises the main bulk of the lesion and is more apparent 24hrs after ILP. None of these groups
reported the presence of preserved hepatocytes within the boundaries of the ILP-induced necrotic lesions, in normal animal liver.

However, this phenomenon of "preserved" hepatocytes on light microscopy, within coagulated and necrotic tissue has been reported after non-contact laser therapy on liver tissue (Brackett et al, 1986; Stern et al, 1988) - the overall appearances of the different zones are similar to those described by others during ILP. Brackett et al (1986) noted, that after irradiating the liver surface with high power laser light (50-100W), the deepest hepatocytes were at a more advanced stage of necrosis than those nearer to the surface (where the temperatures were higher); many of the more superficial hepatocytes appeared structurally undamaged on light microscopy. The authors postulated that these cells were not viable but did not carry out any histochemical analysis. Stern et al (1988) described "heat-fixed" hepatocytes in the zone of coagulative necrosis, which were seen for up to 14 days after non-contact laser therapy. Van Hillegersberg et al (1991) performed non-contact laser therapy to a rat liver tumour model, and found maintenance of tumour structure for up to 36 days afterwards, despite obvious necrosis of surrounding liver tissue; the most peripheral part of this surrounding liver showed more degenerative change than the zone adjacent to the tumour, and this was explained by heat fixation of the latter zone (at higher temperature) and thermal damage to the former zone (at lower temperature). The tumour cells were also assumed to be heat-fixed and non-viable. Dowlatshahi et al (1992) also noted preservation of some tumour cells within a well-defined zone of coagulative necrosis, following water cooled interstitial laser therapy to a rat mammary adenocarcinoma model.

In pathology, tissue is "fixed" primarily so that it is better able to withstand subsequent processing. Fixation is defined as a partial denaturation of tissue proteins so that the tissue and cellular structure is preserved (Bernard, 1974). Autolysis and putrefaction are arrested and structural protein is stabilised; this is associated with disulphide bond formation and a decrease in protein solubility (Hopwood et al, 1984). The most frequently used method of fixation is chemical, using aldehydes such as formaldehyde and glutaraldehyde (Dawson, 1972; Hopwood, 1972). The use of heat as a method of tissue fixation has also been successfully used by several investigators, using temperatures ranging from 45°C to 80°C (Peracchia and Mittler, 1972; Dutt, 1974; Ni et al, 1981); autolysis is said to be almost completely inhibited by heating to 57°C (Drury and Wallington, 1980). Microwave irradiation causes rapid and uniform heating of tissues by thermal agitation of water molecules, and is a useful method of tissue fixation (Mayers, 1970). The optimum temperature for microwave fixation of tissues has been quoted as 70°C (Bernard, 1974), although satisfactory fixation has been achieved at temperatures of 58-62°C (Leong et al, 1985; Login, 1978); however, others have quoted 60°C as optimum for human materials, distortion occurring at higher temperatures and little or no fixation at lower temperatures (Filipe and Lake, 1990). Hopwood (1985) found that mammalian tissues were severely damaged above 65°C, but Schneider et al (1982) found temperatures of 83-95°C suitable
for fixation of brains. This variation in suitable temperatures for tissue fixation is somewhat confusing, and it is likely that different tissues have a different optimum temperature for fixation.

However, this data does indicate that there is a "window" of temperature within which heat fixation of tissues occurs. During ILP, it has been established that a temperature gradient exists in the tissue around the fibre-tip, the maximum temperature rise being adjacent to the fibre-tip, with a gradually decreasing tissue temperature with increasing distance from the fibre-tip (Matthewson et al, 1987). At 2W, the mean temperature recorded at the fibre-tip was 100°C, and 8mm away this dropped to 52°C (Matthewson et al, 1987).

An optimum window of temperature for tissue fixation would be one explanation of the finding and location of the heat-fixed zone of hepatocytes noted in our study: zone 3 would represent the damaged/distorted zone of higher temperatures, zone 4 the optimum fixation zone, and zone 5 the imperfectly fixed zone at the lower temperatures. Zone 6, the most peripheral zone bordering normal liver, shows the features of usual coagulative necrosis and inflammatory response.

Other groups have also noted a relatively mild inflammatory response around laser-induced necrotic lesions, and the paucity of inflammatory cells invading the lesion (Matthewson et al, 1987; Brackett et al, 1986; Van Hillegersberg et al, 1991). This may be due to a combination of reasons. Heat denaturation of proteins and enzymes may result in suppression of any endogenous stimulus. Another possibility is the formation of a physico-chemical barrier to the ingress of neutrophils, because of protein denaturation and loss of permeability or sealing of vessels. The sharp inner rim of the neutrophil band would be consistent with some form of barrier to the ingress of neutrophils.

Other local heating techniques such as RF electrocautery produce similar thermal lesions as ILP, in normal liver; McGahan et al (1992) found active necrosis more peripherally, and structurally intact hepatocytes more centrally, for up to 5 weeks. More conventional hyperthermic temperatures (40-42°C for 65-495 minutes) applied to human livers resulted in no obvious damage on light microscopy of biopsies taken 2 days later (Wills et al, 1976); but on electron microscopy ultrastructural damage of mitochondria, rough endoplasmic reticulum, and Golgi cisternae was noted (Wills et al, 1976).

5.1.5. CONCLUSION

From our data and that of others, it is clear that localised heat treatment of liver can result in in situ fixation of some hepatocytes; this has also been seen in experimental tumour models. This has important clinical implications, since core biopsies are regularly performed to assess response of tumours to heat therapy, the histological assessment being
undertaken usually by light microscopy and H & E staining. Structurally normal looking
tumour cells may result in retreatment of patients, which may be unnecessary if the cells are
not viable, but simply heat-fixed. The diaphorase method used in this study requires fresh
tissue but is otherwise easy to perform, gives clear unequivocal results, and defines the
extent of non-viable tissue exactly, immediately (when H & E assessment is most difficult)
and for at least 3 weeks after ILP. It may be that at some point after ILP, say 2-3 months,
the previously "fixed" hepatocytes look clearly abnormal on H & E staining, and it may
then no longer be necessary to perform histochemical staining. It must also be remembered
that ILP in human livers may not give rise to in situ fixation. This emphasises the need to
perform ILP in humans and to then resect the treated liver tumour surgically, so that careful
histological evaluation can be made.

This study also highlights the importance of other ways of assessing ILP-induced necrosis.
Dynamic CT is non-invasive, and clearly shows devascularised (and hence non-viable)
treated tissue. This is discussed in the next section.
5.2. CT-PATHOLOGIC ASSESSMENT OF ILP-INDUCED NECROSIS IN RAT LIVER

5.2.1. INTRODUCTION

Imaging plays a vital role in ILP, and is needed for treatment delivery, monitoring of tissue damage during treatment, and evaluation of the extent of necrosis afterwards. Ultrasound (US) scanning and magnetic resonance imaging (MRI) have been used experimentally to monitor the tissue changes occurring during and after ILP, but the role of computerised tomography (CT) has been largely ignored.

When treating patients with liver tumours by ILP, CT has been found to be particularly useful for showing tissue changes 24hrs or later following treatment (Amin et al, 1993a). However, in order to fully understand what the changes seen on imaging really mean, a careful correlation between the CT images and the pathology is needed, and this is best done experimentally in animal models. Liver CT can be performed without contrast, during dynamic intravenous bolus contrast enhancement, or by delayed scanning (4-6hrs after intravenous contrast administration) - the optimal technique depending on the type of lesion being imaged (Foley, 1989; Bernardino et al, 1986; Tidebrant et al, 1990).

The aims of this study were to determine: (a) whether the extent of the tissue density changes seen on CT after ILP to rat liver matches the extent of necrosis found pathologically, and (b) which liver CT technique (pre-contrast, dynamic, or delayed) best shows the treated necrotic zone.

5.2.2. METHODS

5.2.2.1. ILP technique: Twenty four male Wistar rats (weight 300-350g) were anaesthetised and ILP performed as described in section 5.1.2.1. The exposure time for laser activation was 200-500s, and was essentially determined by the changes occurring on the liver surface overlying the tip of the fibre; a gradually enlarging circular zone of desiccation and blackening was seen, and when this reached approximately 1cm in diameter the laser exposure was terminated and the optical fibre removed.

5.2.2.2. CT markers: The next step was to place markers at 2 diagonally opposite points on the lobe of liver, so that a line joining these points included the zone of thermal damage. These markers had to be small and sufficiently radio-opaque so as to be easily seen on CT, but without causing artefact. We found that 1mm segments of a 5F angiographic catheter were very suitable markers. The fact that they were hollow allowed easy attachment to the sides of the liver lobe by a 3/0 silk suture. After careful placement of
the markers, the liver lobe was returned to the abdominal cavity, the wound closed and the rats allowed to fully recover.

5.2.2.3. CT technique: The 24 rats were divided into 2 groups, A and B, with 12 rats in each group. Rats in group A had CT scanning performed 24hrs after ILP, and those in group B had CT at 2 weeks after ILP. Within each group, 4 rats were imaged without any contrast, 4 rats had "dynamic" contrast enhanced scans, and the remaining 4 rats had delayed (3-4 hours after contrast) scans. Scanning live rats produced some motion artefact, and so it was decided to scan the rats after sacrificing them, since the image was significantly better in the absence of respiratory motion. The CT density of the liver was assumed to remain unaltered within a few hours of death.

Iodinated contrast (Conray 280, May & Baker Ltd, Dagenham, England) was injected into the femoral vein of the live rat with a 25 gauge needle; the strength of the contrast medium used was 600mg/l/kg which required 0.65-0.75mls of contrast. For delayed scans, the rats were injected with contrast 3-4hrs prior to sacrificing them by carbon dioxide inhalation. For "dynamic" scans, the contrast was injected as a bolus over 10-15s, and the rats killed 15-20s later by a rapid bolus injection of 0.3-0.5mls Expira (pentobarbitone sodium, 200mg/ml, Sanofi Animal Health Ltd, Herts., England) into the femoral vein (the rats dying within 2-5s of the injection). In this way the contrast is "trapped" in the vessels and should give an image analogous to a dynamic CT in a live rat with rapid scanning. The 3 rats in each group which did not have contrast injected were sacrificed by carbon dioxide inhalation.

All rats had CT scans (Siemens, Somatom DR) of their liver within 1-2hrs of death. Each rat was placed supine and scanned in a cephalo-caudad direction. The markers were not seen on the topogram, and so contiguous scans (slice thickness 2mm, zoom factor 4) were performed through the rat liver until both markers were detected (invariably in different slices). The position of the rat was then adjusted in an attempt to image both markers in the same plane, and the scans repeated - this manoeuvre had to be repeated up to 4 times in order to image the correct plane which included both markers, the ILP-induced necrosis and some surrounding normal liver. Once this was achieved, the mean CT density number (in Hounsfield units, HU) of a selected region of interest (ROI) was determined, from both the necrotic lesion and the surrounding normal liver. The ROI of the necrosis was taken from its centre, avoiding the edges, so as to minimise partial voluming effects. Next, the size of the necrosis on the CT scan was measured with callipers from the computer screen, along a line joining the 2 markers.

5.2.2.4. Pathological assessment: Within an hour of the CT scans, a further laparotomy was performed in all of the dead rats, the treated liver lobe resected and placed in 10% buffered formalin for 2-4 days. After fixing, the lobes were carefully sectioned
into 1-2mm slices in a plane parallel to the markers. The section which included both markers was used for measuring the size of the necrotic lesion in the same way as the measurements taken from the CT scans. These pathological measurements were taken by another person (Glenn Spencer) who was unaware of the CT results. The overall morphology of the necrotic lesion seen macroscopically was also compared with its appearance on the CT scans.

5.2.2.5. Statistical analysis: The CT density numbers are expressed as the means of ROI measurements in four rats. The CT density numbers after contrast ("dynamic" or delayed) were compared with the CT density numbers before contrast, in normal liver and necrosis, using the Wilcoxon rank sum test for two independent samples. Kendall’s rank correlation coefficient (tau) was calculated to confirm statistically the association between the size of necrosis on CT and the size of necrosis measured on the pathological specimen.

5.2.3. RESULTS

All of the data on CT density numbers and measurements of necrosis size on CT and pathologically are given in the appendix. Below, are given the means, where appropriate.

All rats survived the ILP procedure and contrast injections. The enhancement technique worked well and Figure 5.6 shows the CT scans of normal rat liver before contrast, and following "dynamic" and delayed contrast enhancement. The typical appearance of a necrotic lesion in a lobe of rat liver 24hrs after ILP is shown in Figure 5.7, with the markers visible at the liver edges on either side of the necrotic lesion. The necrosis was seen as a well-defined, yellow area on the liver surface. A section of the liver lobe in the plane of the markers is shown in Figure 5.8(a) with a corresponding CT image of the same slice in Figure 5.8(b), the markers and necrosis clearly seen.

The size of necrosis measured on CT scan correlated exactly with the actual size of necrosis measured pathologically (in the plane and line of the markers) in 12 cases, and differed by 1-2mm in the other 12 cases (Figure 5.9). The correlation coefficient was tau=0.91, which was statistically significant (p<0.001). All but one of the lesions in which CT and pathologic size did not match exactly had been contrast enhanced (either "dynamic" or delayed) for the CT scans; in 4 cases the measurements on CT were slightly greater than the pathological measurements, the opposite being true in the other 7 cases. The general morphology of any irregular necrotic lesion seen on CT corresponded to its macroscopic appearance pathologically. The pathological specimens 2 weeks after ILP showed generally sharper margins than at 24hrs, macroscopically, although no obvious difference in appearance was seen on the CT scan.
Figure 5.6: CT scans of normal rat liver (a) without contrast, (b) after "dynamic" bolus contrast enhancement, and (c) delayed 3-4hrs after contrast injection. All of these scans were taken at a window level of 80HU and a width of 130HU to show comparable images, and in (b) retention of contrast with the "dynamic" technique used; the optimal window level and width for the "dynamic" scans was 120HU and 250HU, respectively, which is shown in (d) where the vessels can be seen to be enhanced (arrows).
Figure 5.6 (continued)
Figure 5.7: Resected lobe of rat liver 24hrs after ILP. The central ellipsoid area is the zone of necrosis, as it appears on the liver surface. The two white markers can be seen sutured to the liver edges (arrows).
Figure 5.8: (a) Section of rat liver in the plane of the markers, with the central pale area of necrosis clearly seen. There is a small central thrombosed vessel. Markers are indicated by arrows. (b) Corresponding delayed CT scan, the markers being seen as well-defined bright circles (arrows), and the necrosis represented by the relatively low density zone (between cursors, +...+) in the liver. In this case the measurement of the necrosis pathologically corresponded exactly with the measurement on CT (11mm, taken from the anterior margins of the markers).
Figure 5.9: Graph showing the relationship between the size of the necrotic lesion measured on CT with the size measured macroscopically on the pathological specimen, from 24 pairs of measurements. The straight line (y=x) represents exact correlation between CT and pathology. Correlation coefficient, tau=0.91 (p<0.001).
The measurements of the specimens were essentially unaffected by fixing in formalin for 2-4 days. This was evaluated by measurements of the necrotic areas on the surface of the liver lobes in the plane of the markers, immediately after sacrificing the rat and again after fixing, ie. just before sectioning. Either no difference in these measurements were noted, or there was a 0.5mm reduction in size.

Tables 5.1 and 5.2 show the mean values for CT density number of the normal liver and necrotic lesion before contrast, after "dynamic" enhancement, and after delayed scanning, at 24hrs and 2 weeks after ILP, respectively. It can be seen that normal liver was significantly (p<0.05) enhanced after "dynamic" and delayed CT scans, with a mean rise in CT density of 43HU after "dynamic" scans and 16HU after delayed scans, at 24hrs; corresponding figures at 2 weeks were 47HU and 21HU, respectively. The necrotic lesion failed to enhance significantly after "dynamic" or delayed scans, at 24hrs or 2 weeks. The maximum liver-to-lesion contrast (ie. difference in CT density number in HU) occurred after "dynamic" enhancement at 24hrs and at 2 weeks, although contrast between liver and lesion was still sufficient to delineate the extent of necrosis on the pre-contrast and delayed CT scans; this difference is quantified in Tables 5.1 and 5.2.

**Table 5.1:** Mean CT density number of liver and necrosis, and mean difference in CT density number (HU) between liver and necrosis, after pre-contrast, "dynamic" and delayed CT scans at 24hrs after ILP. Individual measurements are given in the appendix (page 209).

<table>
<thead>
<tr>
<th></th>
<th>Pre-contrast</th>
<th>Dynamic</th>
<th>Delayed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>68</td>
<td>111†</td>
<td>84†</td>
</tr>
<tr>
<td>Necrosis</td>
<td>47</td>
<td>49</td>
<td>50</td>
</tr>
<tr>
<td>Difference</td>
<td>21</td>
<td>62</td>
<td>34</td>
</tr>
</tbody>
</table>

†Significant difference in CT density number compared to pre-contrast scan (p<0.05)
Table 5.2: Mean CT density number of liver and necrosis, and mean difference in CT density number (HU) between liver and necrosis, after pre-contrast, "dynamic" and delayed CT scans at 2 weeks after ILP. Individual measurements are given in the appendix (page 209).

<table>
<thead>
<tr>
<th></th>
<th>Pre-contrast</th>
<th>Dynamic</th>
<th>Delayed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Liver</strong></td>
<td>72</td>
<td>119†</td>
<td>93†</td>
</tr>
<tr>
<td><strong>Necrosis</strong></td>
<td>55</td>
<td>59</td>
<td>63</td>
</tr>
<tr>
<td><strong>Difference</strong></td>
<td>16</td>
<td>60</td>
<td>30</td>
</tr>
</tbody>
</table>

†Significant difference in CT density number compared to pre-contrast scan (p<0.05)

5.2.4. DISCUSSION

This study confirms that in normal rat liver laser-induced necrosis after ILP is well seen by CT, and the extent of necrosis judged by CT matches the extent of necrosis found pathologically. The latter was evaluated macroscopically, since this is easily done and the margins of necrosis correspond to the margins seen microscopically (section 5.1). We have also demonstrated that the greatest contrast between normal liver and laser-induced necrosis is achieved after "dynamic" bolus contrast enhanced CT.

A slight mismatch between CT and pathology occurred in 12 necrotic lesions, which was no greater than 1-2mm. This may partly be explained by an inevitable small error occurring when measuring the lesions and in getting the planes of imaging and sectioning to correspond perfectly. Eleven of these 13 lesions had contrast enhancement, in 7 CT underestimated and in 4 it overestimated the size of necrosis. Histological evaluation of the periphery of necrotic lesions has shown fairly wide interstitial spaces as well as some damaged, but patent small blood vessels (section 5.1; Tracz et al, 1993); contrast medium can therefore enter the periphery, and result in some error in locating the edge of the necrosis on "dynamic" or delayed CT scans. A further factor which may result in difficulty in accurately defining the margins of a necrotic lesion adjacent to high density liver (from contrast enhancement) is computer averaging of high and low density pixels in the same slice thickness ("partial voluming") (Sundin et al, 1992); this could be a particular problem with "dynamic" scans. Clinically, these aspects are likely to be much less of a problem, with the necrotic lesion being several centimetres in diameter (using multiple fibres), and perfusion of contrast and partial voluming at the edges likely to be insignificant compared to the size of the necrosis.
The reason for imaging 2 groups of rats at 24hrs and at 2 weeks was to evaluate whether the CT appearance of the lesion changed with time. This was not found to be the case. Although macroscopically the necrosis had sharper edges at 2 weeks compared to 24hrs, such a change is not expected to be apparent on the CT scans, since the necrosis is already fairly well-defined by 24hrs. A better pathological definition of necrotic boundaries has also been found at 14 days compared to 24hrs following ILP to brain tissue (Tracz et al, 1993).

The "dynamic" contrast enhancement technique for rat liver CT described is particularly useful since it removes the problems of image degradation by respiratory motion, as well as allowing the whole liver to be scanned in the same phase of enhancement. Such dynamic CT in a live rat would be very difficult since maximum enhancement is likely to be over in a fairly short time, and before the whole liver has been scanned on a conventional CT scanner. In patients, peak hepatic enhancement occurs over the first 2-5 minutes after a rapid bolus of contrast is injected intravenously over 1-2 minutes (Foley, 1989); in rats the injection is over in 10-15s, and peak enhancement is likely to be over in well under 1 minute. Our technique of "dynamic" enhancement increased the CT density number of normal rat liver by 45-50HU, which is comparable to an increase of 40-60HU in patients having dynamic liver CT (Tidebrant et al, 1990).

In the preliminary work which demonstrated motion artefact when scanning live rats, liver CT density numbers were taken from two rats immediately after injecting contrast, and from another two 3-4hrs after contrast. This showed a maximum increase in CT density numbers which was similar to those seen in the dead rats, indicating that contrast dissipation and delivery to the liver is unlikely to be significantly altered by the post-mortem state. Also, the contrast itself was unlikely to have any affect on the extent of necrosis, since all contrast was administered 24hrs or more after ILP; maximum histological changes have already occurred by this time (Matthewson et al, 1987).

Accurate comparisons of findings on imaging with pathological specimens are vital to really understand what the images mean. This can only reliably be done by comparing images and specimens from the same plane, which can be a notoriously difficult task. Many authors tend to ignore a mismatch of planes and still claim good correlation between imaging and pathology. For a technique which is locally destructive, such as ILP, it is essential to be able to accurately define the extent of damage. Experimental studies correlating US (Stieger et al, 1992a) and MRI (Tracz et al, 1992; Anzai et al, 1992) of ILP-induced liver necrosis with pathology have found good correlation between the sizes on imaging with the sizes pathologically, but none of these have used any markers to define the plane being imaged. An alternative to using markers is to fix the animal being imaged to a board, apply a series of labelled markers to the sides of the board, image with CT or
MRI, freeze the animal so that all tissue solidifies, and then slice the whole animal in the appropriate plane (Sundin et al, 1992).

5.2.5. CONCLUSION

This study has confirmed that the extent of tissue density changes on CT in rat liver after ILP match the extent of necrosis seen pathologically, and that the optimal CT technique for evaluating laser-induced necrosis is dynamic contrast-enhanced scanning.

Although good agreement between CT and pathology has been shown for evaluating ILP-induced necrosis in normal liver, this may not necessarily be the case when treating tumours. The additional problem arises of not only having to differentiate necrotic tissue from normal tissue, but also being able to identify any residual or recurrent tumour. Clinically, dynamic CT appears promising since laser-necrosed tumour and normal liver becomes completely non-enhancing after ILP, untreated liver enhances normally, and untreated tumour continues to enhance only partially (Amin et al, 1993a). However, what is needed is a careful correlative study to verify these findings; ideally, a patient with a liver tumour should be treated with ILP, imaged carefully, and then the treated tumour surgically resected, so as to allow comparison between the images and pathological specimen. Achieving comparison between exactly the same planes would obviously be difficult in the clinical setting, but considerable useful information could still be obtained about the general features of treated, untreated or recurrent tumour. Although a clinical evaluation of this sort would be ideal, it is likely to be more practical to perform such a study in an animal liver tumour model. This is clearly of importance, since the aim is to destroy tumour with laser therapy, and an imaging-pathologic correlation following ILP to liver tumour is crucial for a better understanding of what the changes on imaging really mean.
SECTION C: CLINICAL WORK

CHAPTER 6: INTERSTITIAL LASER PHOTOCOAGULATION OF LIVER METASTASES

6.1. Introduction

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   6.2.1. Patient details
   6.2.2. Technique of ILP
   6.2.3. Imaging techniques
   6.2.4. Statistical analysis

6.3. Results
   6.3.1. Treatment sessions
   6.3.2. Imaging results
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   6.3.4. Patient response
   6.3.5. Complications
   6.3.6. Survival analysis

6.4. Discussion
   6.4.1. ILP technique
   6.4.2. Imaging
   6.4.3. Evaluation of response
   6.4.4. Safety
   6.4.5. Patient survival
   6.4.6. Conclusions
6.1. INTRODUCTION

This section describes the clinical application of ILP to treat patients with liver metastases. A total of 31 patients have been treated. Ten of these patients had at least part of their treatment prior to the current period of work for this thesis, and the early results of ILP on these patients have been previously reported (Steger et al, 1989a; Masters et al, 1992). However, a more detailed analysis of these 10 patients has been undertaken for the purposes of this thesis, including a re-evaluation of the CT findings and a survival analysis. In addition, 5 of the 10 patients had their ILP treatment continued during the work for this thesis. Therefore, at least 26 patients reported here were treated and evaluated during the period of study for this thesis, and all 31 patients included in the data analyses.

Several previous clinical studies have used ILP to treat patients with liver tumours, and shown that tumour necrosis can be effectively achieved. However, patient numbers have been small and the techniques used have varied. Clinical experience remains very limited, and ILP continues to evolve and improve.

The purpose of this study was to perform a detailed assessment of the potential clinical role of ILP for treating liver metastases in a much larger group of patients than previously reported, and to undertake a critical evaluation of the imaging methods used, namely, ultrasound, CT and MRI.

6.2. METHODS

6.2.1. PATIENT DETAILS

Thirty one patients (11 female and 20 male; median age 65 years, range 28-77 years) with liver metastases were treated with ILP. The primary sites were: 25 colorectal; 1 stomach; 1 oesophagus; 1 renal; 1 colorectal and breast; 1 small bowel carcinoid; 1 pancreatic islet cell (non-functioning). Patient details are summarised in Table 6.1 (at end of results, page 180). All patients were asymptomatic, except the patient with small bowel carcinoid who complained of intermittent diarrhoea. Inclusion criteria were flexible, particularly in the early stages of the study, but patients with evidence of extra-hepatic disease were excluded. Preferred criteria were: less than 5 metastases with none measuring more than 4-5cm. Some larger lesions were included in the earlier part of the study when the objective was to evaluate the extent of thermal damage which could be induced by ILP. Patients either had inoperable liver metastases (affecting both lobes of the liver, or solitary lesions adjacent to major vessels), were unfit for surgery, or had refused an operative resection of their liver tumour. Twenty three patients received some form of systemic chemotherapy before or
after ILP treatment (eight of these patients had chemotherapy both before and after ILP); for patients with colorectal liver metastases, this was invariably a combination of 5-fluorouracil and folinic acid.

This study had been approved by the local Ethical Committee and all patients gave informed consent.

All patients had pre-treatment CT scans (see below) of the liver performed within a few days of treatment, as well as serum biochemical (electrolytes, urea and liver function tests) and haematologic (Hb, platelets and prothrombin time) evaluation before and after ILP treatment. Serum carcinoembryonic antigen (CEA) levels were also measured as a tumour marker in patients with colorectal metastases; blood samples were taken before each ILP treatment and at various times following treatment (usually 1-2 months). Urinary 5-hydroxyindoleacetic acid (5-HIAA) levels (24 hour) were measured in the patient with metastatic carcinoid, just before each treatment.

6.2.2. TECHNIQUE OF ILP

Immediately prior to the procedure patients received diazepam (5-15mg) and pethidine (50-100mg) intravenously. Prophylactic antibiotics (cefoxizime 1.5g and gentamicin 80mg) were also administered intravenously, and continued (every eight hours) for 24 hours after the procedure. Ultrasound scanning was performed with a 3.5MHz or 5MHz transducer (Aloka 650, Tokyo, Japan). Eight tumours (in six patients, all smaller than 2cm in diameter) seen on CT, could not definitely be identified on ultrasound; four of these were treated under CT guidance and 4 left untreated. After localisation of the tumour with ultrasound (or CT in 4 cases), 5-20mls of 1% lignocaine was infiltrated into the abdominal wall at the intended puncture site, and down to the liver capsule. This was followed by an ultrasound-guided core biopsy of the tumour to be treated using a spring-loaded Biopty instrument (Bard, Covington) with an 18G Trucut needle. At least one tumour in each patient was biopsied before treatment, to confirm histologically the presence of metastatic disease. Four (more recently up to 8) hollow 19G needles were then inserted under ultrasound or CT guidance into the tumour at the site of intended necrosis (Figure 6.1). The needle tips were positioned about 1-1.5cm apart in the deepest part of the tumour, since this distance has been found to be the most suitable to ensure necrosis of intervening tissue (Steger et al, 1992). For small tumours measuring 1-1.5cm, only 2 needles per tumour were required, and in those tumours measuring 0.5cm 1 needle was used.

A freshly cleaved, sterile 0.2mm silica clad optical fibre from a 1x4 star coupler fibre splitter (Canstar, Ontario, Canada) was inserted down each of 4 needles and the needles withdrawn slightly, so that 3-4mm of bare fibre tip lay within the tumour (Figures 6.2 and 6.3). A bare fibre-tip rather than a diffuser tip was used because it had previously been
shown that the latter offers no advantage in terms of size of necrosis produced or efficiency of light delivery (van Eeden et al, 1988). The tumour was treated with laser light (wavelength 1064nm) from a continuous wave Nd:YAG laser (Flexilase, Living Technology, Glasgow) at a power of 2W per fibre for 500 seconds (total energy 4000J if four fibres used). The maximum power which could be transmitted down each fibre was 2W, higher powers causing damage to the coupler; an exposure time of 500s was chosen because experimental work using the 4-fibre system showed that the maximum necrosis occurred with 1000J (2W x 500s) of energy (Steger et al, 1992). More recently a portable diode laser (Diomed-25, Diomed, Cambridge, UK) has been used (Figure 6.4) with its own 1x4 coupler system, capable of delivering 1.5-2W per fibre; this laser was used for all of the CT-guided ILP sessions. Ensuing tissue changes were monitored during treatment, with ultrasound.

The needles and fibre tips were then carefully repositioned by withdrawing them approximately 1-1.5cm and the treatment repeated. This was done up to four times at one session, depending on the size of the tumour and the thermal changes seen on ultrasound. For tumours less than 3cm maximum diameter, this manoeuvre allowed optimal coverage in most cases. However, for larger tumours, in order to achieve greater areas of necrosis, the needles had to be withdrawn and replaced in a different part of the tumour. This was often limited by the degradation of the ultrasound image by the echogenic area already treated. This problem has been partly overcome in more recent cases by placing 8 needles in the appropriate sites within the tumour prior to starting treatment and then performing ILP via the 2 sets of 4 needles, one after the other (Figures 6.1 and 6.2). Some of the earlier tumours were treated before the Canstar fibre splitter was available, and in these cases 1 to 3 laser fibres were used, depending on the tumour size and accessibility, and activated consecutively rather than concurrently. Treatment of up to 3 tumours was frequently undertaken at the same session, with 2 to 8 needles per metastasis, and a maximum of 12 needles per session. The total procedure time varied from 1 hour to 2.5 hours.

Three patients had ILP performed under general anaesthesia. In 2 of the patients, this was because the tumours lay adjacent to the liver capsule (next to the peritoneum) and previous ILP treatment had caused severe local pain; the third patient had had a marked elevation in blood pressure during the previous ILP treatment session (see section 6.3.5).
Figure 6.1: Photograph of needles being inserted percutaneously under ultrasound guidance. Eight needles are in place, with the ultrasound transducer next to them.

Figure 6.2: Patient being treated by ILP. Optical fibres can be seen entering four needles. The patient is wearing protective goggles and the Nd:YAG laser is seen in the background.
Figure 6.3: 1x4 star coupler. The single input fibre is seen entering the coupler, and 4 output fibres exiting. This device splits the laser beam equally into 4 separate beams.

Figure 6.4: The new portable diode laser, which is simple to use and about the size of a typewriter. This laser was used for the CT-guided ILP sessions.
6.2.3. IMAGING TECHNIQUES

6.2.3.1. Ultrasound
Abdominal ultrasound scanning was performed just prior to ILP, as described above, to confirm the site and size of the liver tumour to be treated, and then used for guided percutaneous biopsy of the tumour, followed by multiple needle insertions into the tumour. During ILP, thermal changes around the needle/fibre-tips were monitored with ultrasound, as was the needle-tip repositioning after each 500s cycle of ILP.

Ultrasound was again performed shortly after ILP, and at various times (weeks to months) after the procedure; it was also used for guided biopsies to histologically assess the treated lesions.

6.2.3.2. Computed tomography (CT)
Prior to ILP, CT scans (Somatom DR, Siemens Medical Systems, Erlangen, Germany) of the liver were performed in order to determine the site, size and number of liver metastases, so that ILP treatment could be properly planned. The CT protocol included non-contrast, dynamic contrast enhanced and delayed (several hours after contrast) scans, with the images zoomed to the liver. Dynamic CT was performed after a rapid intravenous bolus (1-2ml/s) of 150mls of iodinated contrast medium (iohexol, 350mg I/ml); scanning was commenced 50-60s after the start of the contrast bolus. The scan time was 4s per slice with an interscan delay of 12s, giving 4 scans per minute. All scans were contiguous with a slice thickness of 8mm, and the whole liver was scanned in 5-6 minutes. Delayed CT scans were performed 2-3 hours after the injection of contrast medium.

Of the 4 patients who had CT guided needle placement for ILP, 2 had dynamic CT to help localise the tumour, and so further dynamic CT immediately after treatment could not be performed. The other 2 patients had the needles inserted into the tumour using non-enhanced CT, and so dynamic CT was performed immediately after ILP. In these latter 2 patients, dynamic CT was again performed 24 hours later.

All other patients had dynamic CT after each ILP session, either at 24hrs (83 treatment sessions) or 72hrs (18 treatment sessions, when patients were treated just before a weekend) to evaluate the extent of laser-induced necrosis. Early in the course of this study some patients (after 15 of the early treatment sessions) had CT assessment from 6 weeks to 3 months after ILP. The interpretation of these scans is likely to represent an underestimation of the extent of initial necrosis because of resorption of the necrotic tissue or tumour overgrowth. Six patients had pre-contrast and delayed CT scans, as well as dynamic, after ILP, in order to confirm that the dynamic scans were the most suitable for evaluating laser-induced necrosis. The 2 patients with pancreatic islet cell and small bowel
carcinoid primaries had some hypervascular liver metastases, and therefore routinely had a pre-contrast, dynamic, and delayed CT scans after ILP treatment.

Laser-induced necrosis was assessed by comparing the dynamic pre and post treatment CT scans; these were found to be more useful than the non-contrast and delayed scans for this purpose. Laser-induced necrosis was differentiated from spontaneous tumour necrosis by looking for new areas of non-enhancement (indicating avascularity) on the post treatment dynamic CT scan. Areas of the lesion which still enhanced were assumed to indicate residual viable tumour. Because of the very irregular margins of some lesions as well as respiratory variation between scans, accurate comparative volume measurements of tumours and presumed necrotic zones were not possible. Treatment effect as seen on CT was therefore graded by two radiologists (Z Amin and JJ Donald, or Z Amin and WR Lees) as follows: grade I necrosis - 100% of tumour avascularised; grade II necrosis - greater than 50% of tumour avascularised; grade III necrosis - less than 50% of tumour avascularised. These percentages were calculated by dividing the estimated volume of tumour necrosis on the post-ILP CT by the estimated total tumour volume pre-ILP (the volumes simply defined as the product of the 3 largest perpendicular diameters of the lesion on CT).

Biopsies of previously treated areas were undertaken frequently, using an 18G Trucut needle under ultrasound guidance to check histologically for the presence of necrotic tissue or residual/recurrent tumour.

If the post-treatment CT scan showed residual tumour then the patients were retreated within 1 to 4 weeks. If no residual tumour was identified, ie. a grade I necrosis, then the CT scan was repeated at 2 months to look for any evidence of recurrence. For patients with large (5.5-15cm) tumours (9 lesions treated early in the study), the aim was to demonstrate the feasibility of ILP by debulking tumour, and control tumour growth rather than to completely ablate the whole tumour. For this reason some patients had further treatments up to 8 months after their initial treatment, when there was tumour re-growth.

In patients who had frequent CT scans at varying intervals post-ILP a careful analysis of the images was performed in order to determine the optimal time at which to scan patients. Two patients had CT scans at 24hrs, 72hrs and 1 week post-ILP. Another 2 patients had ILP treatment at 1 to 3 week intervals for up to 2 months, treating different lesions, with CT scans after each treatment. This allowed a more detailed analysis of sequential CT scans.

6.2.3.3. Magnetic resonance imaging (MRI)

MRI was performed before and at various times after ILP, in addition to the CT scans, in a small number of patients, to determine whether, using standard sequences, it provided any
additional useful information when evaluating the effects of ILP. Three patients had a
detailed MRI assessment of their liver tumours before, 24hrs, 2 weeks, and 6 weeks after
ILP, using a variety of sequences. Another 3 patients had MRI at various times after ILP.
MR imaging was performed using a 1.0T super-conducting system (Siemens). The liver
was imaged in the axial plane, using a body coil with the following sequences:
(a) Spin-echo T1-weighted, with ECG triggering. TR dependent on heart rate (approx.
600-700ms), TE 15ms. The field of view (FOV) was 450mm, and the image matrix
192x256 (6/8 rectangular FOV applied). 8mm contiguous slices were taken, with 3 signal
averages, and a total imaging time of approximately 6 minutes.
(b) Spin-echo T2-weighted. TR 3000ms, TE 45-90ms. FOV 450mm, image matrix
192x256 (6/8 rectangular FOV applied). 8mm contiguous slices, 1 signal average, and
total imaging time 9-10 minutes.
(c) Rapid acquisition spin-echo (RASE), T1-weighted breath-holding sequence. TR
200ms, TE 20ms. FOV 450mm, image matrix 128x256 (6/8 rectangular FOV applied).
10mm contiguous slices, 1 signal average and half-Fourier sampling, allowed an imaging
time of 18 seconds. This was repeated immediately after an intravenous injection of
approximately 10mls of gadolinium (0.1mmol/kg), and then scanning 1, 3, 5, and 10
minutes following the injection. The short scan intervals meant that the whole liver could
not be imaged in the same phase of contrast enhancement, and so only a few image slices
were taken, to include the tumour.
(d) Turbo-FLASH, gradient echo breath-holding sequence. TR 6.5ms, TE 3ms, flip angle
10°. FOV 400mm, image matrix 128x128. 10mm contiguous slices, 1 signal average,
total imaging time 3 seconds. Rapid scanning following gadolinium was also performed,
as in (c) above.
The liver-to-lesion contrast produced by each of these sequences was evaluated
subjectively, before and after ILP, and following rapid gadolinium enhanced scanning.

6.2.4. STATISTICAL ANALYSIS

The Wilcoxon signed rank test was used to compare CT attenuation numbers in Table 6.2;
a difference in the mean CT density of at least 10HU was taken to indicate clinical
relevance. Life table analysis (Kaplan-Meier method) was performed on the patient
survival data.

6.3. RESULTS

6.3.1. NUMBER OF TUMOURS AND TREATMENT SESSIONS

The 31 patients had 93 liver metastases treated by ILP (Table 6.1). In each patient 1 to 12
(median 3) tumours measuring 0.5 to 15cm (median 2.0cm) in maximum diameter, were
treated. No tumours were larger than 6cm in diameter, except in 4 cases when they measured 8, 8, 9, and 15cm. These tumours were treated early in the course of this study, and patients with such large tumours were later not recruited.

There were 101 patient-treatment sessions (1 to 8 sessions per patient, median 3) and 147 tumour-treatments (since some tumours were treated several times). The total energy used at each session varied from 3000J to 34000J (median 16000J); the energy used per tumour was 2000J to 32000J (median 12000J), smaller tumours generally requiring less laser energy.

On three occasions (twice with patient no. 8, and once with patient no. 23 from Table 6.1), there were technical problems with aligning the input fibre of the 1x4 Canstar coupler to the output beam of the Nd:YAG laser - this resulted in poor output power from each fibre. Attempts to correct the mal-alignment increased the treatment time by 30-60 minutes, but even then the tumours still received suboptimal treatment, necessitating a further ILP session at another date.

6.3.2. IMAGING RESULTS

6.3.2.1. Ultrasound

The majority of the tumours were seen on ultrasound just prior to ILP; the pre-treatment CT scans often helped to increase the confidence with which tumours were detected on ultrasound, with respect to the tumour location. Eight tumours could not be identified on ultrasound, even though the CT scan clearly showed their position in the liver. On the whole, the needle-tips were clearly seen with ultrasound, allowing accurate guidance to the desired target area. In cases where the tumour was echogenic, or in the presence of tumour calcification, or when retreatning a previously treated lesion, the needle-tip localisation was more difficult and so inevitably less accurate. The location of the tumour also influenced the accurate placement of the needle-tips into the desired part of the tumour to be treated, this being more difficult in those tumours situated cranially and anteriorly in the right lobe, or superficially and partly obscured by overlying ribs.

During treatment, ultrasound changes were seen in all tumours treated, which were similar to the changes seen experimentally in animal liver (Dachman et al, 1990; Steger et al, 1992a). After a delay of about 100s, there was a gradually expanding and coalescing hyperechoic zone around each fibre tip resulting from tissue water boiling and microbubble formation. This gave an indication of the extent of tumour treated. Complete tumour coverage and hence a potentially complete necrosis was assumed when the whole tumour was occupied by the echogenic zone (Figures 6.5 and 6.6). However, the margin of the echogenic zone was usually irregular and poorly defined, and so these changes served only as a rough guide to the extent of necrosis, especially when treating larger tumours (greater
than 3 cm). Echogenic linear streaks (Figure 6.7) were frequently seen radiating from the treatment area, and thought to be due to conduction of heat and microbubbles along tissue planes and vessels (Figure 6.8). After 400s of treatment, a plateau effect was seen, with only slight further expansion of the echogenic zone. One to two minutes after completion of treatment, the brightness of the echogenic area decreased, and it became more heterogeneous (Figure 6.5d).

Subsequent follow-up ultrasound 1 week or more after ILP showed a solid heterogeneous lesion (Figure 6.9) in all but 5 cases in which there was a mixed solid and cystic lesion (Figure 6.10) - the cystic component gradually decreased and disappeared by 2 months in 1 patient, and persisted at about the same size in another 2 patients (follow-up 11 and 17 months). A further 2 patients received active treatment for the cystic collections (see section 6.3.5). In all other cases, the heterogeneous treated lesion had bright linear tracks within it which were thought to represent tissue charring around the sites of the fibre-tips (Figure 6.9). Residual untreated tumour in a previously partially treated lesion was difficult to identify on ultrasound, since treated and untreated tumour had similar ultrasound characteristics.

6.3.2.2. Computed tomography
The pretreatment CT scans showed hypovascular liver metastases in all cases, except the patients with islet cell and carcinoid primaries, who had hypervascular metastases; in the former, the best pretreatment CT technique was dynamic scanning, and in the latter it was delayed scanning.

In the two patients who had ILP under CT guidance followed immediately afterwards by dynamic CT scans, there was only a vague low density zone seen in the treatment site which partially enhanced. However, dynamic CT scans taken at 24hrs or 72 hrs after ILP showed treatment effects as well-defined new areas of non-enhancement (indicating laser-induced avascularity). This non-enhancing zone was clearly differentiated from normally enhancing adjacent liver parenchyma and partially enhancing tumour (Figure 6.11), and was assumed to represent laser-induced necrosis. Core biopsies from non-enhancing and partially enhancing zones confirmed the presence of necrotic tissue and viable tumour, respectively (see section 6.3.3 below). Examples of a grade I tumour response (100% necrosis of tumour volume) are shown in Figures 6.12 and 6.13.

Pre-contrast and delayed CT scans gave no additional information to the dynamic scans in evaluating ILP-induced necrosis. On the pre-contrast scans the density of the treated tumour (which is denatured, necrotic, and coagulated) is similar to untreated tumour, and therefore cannot be differentiated. On delayed images, the contrast between residual or necrotic tumour and normal liver is not as good as with dynamic scanning, except with hypervascular tumours (2 patients in this study) (Bressler et al, 1987).
Figure 6.5: (a) Ultrasound scan of the liver showing a 2.5cm hypoechoic metastasis (+....+) in the right lobe, adjacent to the gallbladder. (b) After 200s of ILP an expanding echogenic zone is seen. (c) After 500s of ILP the echogenic zone "covers" the tumour completely. (d) Two minutes following ILP the lesion becomes more heterogeneous.
Figure 6.6: (a) Liver ultrasound showing an echogenic tumour (+...+) adjacent to the diaphragm (arrow). (b) After ILP, the tumour has been occupied by an echogenic zone. The needle shafts are seen to the right of the image.

Figure 6.7: (a) Ultrasound scan showing a liver metastasis (+...+) near the gallbladder (G). The bright spot in the tumour represents a needle-tip. (b) After ILP, the tumour is occupied by an echogenic zone, with irregular streaky margins.
Figure 6.8: Trail of microbubbles (arrow) seen travelling along a hepatic vein towards the inferior vena cava (I).
Figure 6.9: Ultrasound appearance of a treated tumour (+...+) 1 month after ILP, showing a solid heterogeneous lesion with bright linear tracks (thought to be charred tissue).

Figure 6.10: Ultrasound of another treated tumour 1 month after ILP, showing a mixed cystic (C) and solid (S) lesion.
Figure 6.11: (a) Dynamic CT scan of the liver showing a 5.5cm metastasis in the right lobe. (b) 24hrs following ILP there is a well defined non-enhancing area in the medial half of the tumour, indicating treatment-induced necrosis. The two small areas of vacuolation represent the sites of the fibre tips.
Figure 6.12: (a) Dynamic liver CT. There is a 3.5x2.0cm metastasis in the right lobe of the liver. (b) 24hrs following ILP there is a large area of necrosis replacing the tumour. No evidence of residual tumour, indicating a grade I necrosis.
Figure 6.13: (a) Dynamic liver CT showing a 1cm hypovascular metastasis in the right lobe of liver adjacent to the kidney. (b) After ILP, the tumour and a margin of normal liver have been devascularised (a grade I necrosis).
The mean CT attenuation number of a treated lesion remained essentially unchanged in the pre-contrast, dynamic and delayed CT scans, whereas that of the surrounding normal liver increased following contrast (Table 6.2).

Table 6.2: Mean CT attenuation numbers (HU) of six avascularised lesions following ILP. The individual data points are given in the appendix.

<table>
<thead>
<tr>
<th></th>
<th>Mean CT density (HU)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-contrast</td>
</tr>
<tr>
<td>Lesion</td>
<td>43</td>
</tr>
<tr>
<td>Liver</td>
<td>56</td>
</tr>
</tbody>
</table>

The difference between the pre-contrast versus dynamic, and the dynamic versus delayed columns was significant (p<0.05) for the liver. For the necrotic lesion, the difference of the means was less than 10HU, and so not of practical relevance.

Sequential CT analysis was performed to determine when the size of the treatment-induced necrosis will be maximal, and hence the best time to perform the post-ILP CT scan. Several patients had a CT at 72hrs post-ILP. These scans showed a similar lesion size and level of non-enhancement as the 24hr scans. Scans taken 1 week or more after treatment of 4 larger tumours (3-3.5cm in diameter) demonstrated the appearance of a peripheral enhancing rim around the avascularised area (Figure 6.14). In one case this rim increased in size by 2 months, but the patient was not available for biopsy; in another patient, who had chemotherapy after ILP, the rim disappeared by 6 weeks post-ILP; in the remaining 2 patients, biopsies of the rim showed residual tumour in one, and liver tissue with inflammatory changes only in the other. For smaller tumours, an enhancing rim was not seen, and scanning at various intervals after ILP did not give any additional information to the 24hr or 72hr post-ILP scan, although the devascularised area was often better defined on scans later than 2 weeks. There was invariably some reduction in size of the devascularised zone after 2 weeks, either by resorption and replacement with normal liver, or by tumour ingrowth. Further details of follow-up scanning are given below, in section 6.3.3.

6.3.2.3. Magnetic resonance imaging
In the 3 patients who had pre-treatment MRI, the liver metastases were identified as areas of altered signal intensity (overall decrease on T1 weighted sequences, and increase on T2 weighted sequences), but they were not as clearly seen as with dynamic CT scanning (Figures 6.15 and 6.16).
Figure 6.14: (a) Dynamic liver CT. Prior to ILP there is a 5cm deposit lying anterior and lateral to the IVC. Two further deposits are seen anterior and lateral to this. (b) Post-ILP most of the tumour is non-enhancing consistent with necrosis. The anterior lesion has also been treated. (c) One week later there is an enhancing rim in the postero-lateral aspect of the lesion (arrowed); this is likely to represent recurrent tumour.
Figure 6.15: Effects of ILP as seen on MRI. (a) Liver MRI before ILP (T1 weighted spin echo sequence; TR/TE=719/15), showing a slightly low signal intensity metastasis adjacent to kidney (arrows). (b) T2 weighted liver MRI of same lesion before ILP, seen as a higher signal intensity area (TR/TE=3000/90). (c) Dynamic CT showing the low density tumour much more clearly, before treatment. continued on next page....
Figure 6.15 (continued): (d) After ILP, on T1 weighted sequence, the treated area is of lower signal intensity overall but with a heterogeneous appearance (TR/TE=719/15). (e) T2 weighted sequence after ILP shows a low signal intensity lesion with a high signal intensity rim (TR/TE=3000/90). (f) After gadolinium enhancement and using a breath-holding T1 weighted rapid spin echo sequence (RASE, TR/TE=200/20), the treated area is clearly seen as a low signal intensity lesion with a thin enhancing rim.
Figure 6.16: Effects of ILP as seen on MRI. (a) Liver MRI before ILP (T1 weighted spin echo sequence; TR/TE=719/15), with a metastasis poorly seen in the right lobe, anteriorly (arrow). (b) T2 weighted liver MRI of same lesion before ILP, seen as a higher signal intensity area (TR/TE=3000/90). (c) Dynamic CT showing the low density tumour much more clearly, before treatment. continued on next page....
Figure 6.16 (continued): (d) After ILP, on T1 weighted sequence, the treated area has a heterogeneous appearance (TR/TE=719/15). (e) T2 weighted sequence after ILP shows a low signal intensity lesion with a high signal intensity rim (TR/TE=3000/90). (f) After gadolinium enhancement and using a breath-holding T1 weighted rapid spin echo sequence (RASE, TR/TE=200/20), the treated area is clearly seen as a low signal intensity lesion.
Following ILP, pre-contrast T1 weighted spin echo images showed the treatment effects as a zone of lower signal intensity after ILP (Figure 6.15 and 6.16) in all patients; in 2 patients there were high signal components within the low signal intensity zone. T2 weighted spin echo images showed a more pronounced low signal intensity zone surrounded by a high signal intensity rim (Figure 6.15 and 6.16). Gadolinium enhanced MRI showed the treated area clearly as a uniformly non-enhancing low signal intensity zone. This occupied only a small part of the high signal intensity rim seen on the T2 weighted images indicating that the latter mostly represents oedematous but viable tissue. On one occasion, an enhancing rim was seen following gadolinium enhancement (Figure 6.15).

With the sequences used, the treated tumour could not be distinguished from untreated tumour. Although rapid MR after gadolinium did show the necrotic zone clearly, untreated tumour was not well enough defined on the MR images even before treatment, and so MR was not found to be useful in differentiating between treated and untreated tumour.

6.3.3. TUMOUR RESPONSE

The final grade of necrosis achieved for each tumour, as assessed by dynamic CT, is shown in Table 6.1. All of the tumours treated had some evidence of laser-induced necrosis of at least 10% of tumour volume. Table 6.3 shows the number of tumours in which a grade I, II, or III necrosis was achieved.

Table 6.3: Number and sizes of tumours with a grade I, II, or III necrosis. (Data from Table 6.1).

<table>
<thead>
<tr>
<th>Necrosis grade*</th>
<th>n (%)</th>
<th>Median tumour size (cm)†</th>
<th>Median number of treatments per tumour†</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>51 (55)</td>
<td>1.7 (0.5-3.5)</td>
<td>1 (1-2)</td>
</tr>
<tr>
<td>II</td>
<td>32 (34)</td>
<td>3 (1-8)</td>
<td>2 (1-5)</td>
</tr>
<tr>
<td>III</td>
<td>10 (11)</td>
<td>5.5 (4-15)</td>
<td>2.5 (1-5)</td>
</tr>
</tbody>
</table>

n = number of tumours.

*Grade I necrosis = 100% avascularisation of tumour on dynamic CT scanning; grade II necrosis = more than 50% avascularisation of tumour on dynamic CT scanning; grade III necrosis = 10-50% avascularisation of tumour on dynamic CT scanning.

†Numbers in parentheses define the range.
Table 6.4 shows the results obtained in tumours under 4cm in maximum diameter compared with those measuring 4cm or over.

Table 6.4: Results of ILP in tumours less than 4cm compared with those 4cm or larger. (Data from Table 6.1).

<table>
<thead>
<tr>
<th>Tumour size (cm)</th>
<th>n</th>
<th>Number of treatments per tumour (median)</th>
<th>Necrosis grade achieved</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>I</td>
</tr>
<tr>
<td>&lt; 4</td>
<td>72</td>
<td>1-3 (1)</td>
<td>51</td>
</tr>
<tr>
<td>&gt; 4</td>
<td>21</td>
<td>1-5 (3)</td>
<td>0</td>
</tr>
</tbody>
</table>

n = number of tumours

These tables show that grade I necrosis occurred only in smaller tumours no greater than 3.5cm in diameter, and required no more than two ILP treatments. All tumours less than 4cm in size had a grade I or II necrosis, compared with a grade II or III necrosis in all tumours larger than 4cm in diameter; the smaller tumours also required fewer treatments per tumour (median of 1 versus 3 for larger tumours). Of those tumours less than 4cm in diameter, grade I necrosis was achieved in 71% (51 of 72 from Table 6.4). Considering only those tumours measuring 2cm or less in diameter, grade I necrosis was achieved in 75% (36 of 48, data from Table 6.1). Once a grade II or III necrosis was achieved, progress to a grade I necrosis was only possible in 4 tumours (all 2.5cm or 3cm in size) on further ILP treatment. Overall, 89% (83 out of 93) of tumours treated by ILP showed a greater than 50% reduction in tumour volume (grade I or II), that is, replacement by necrotic tissue, as assessed by CT.

Most of the tumours which had a grade I necrosis have so far been followed up for a relatively short time, and they have on the whole remained fairly well-defined avascular lesions, with no definite evidence of recurrent tumour. They have stayed either the same size or more usually, undergone a slight reduction in size on follow-up scans; complete disappearance was unusual. Some representative examples are shown graphically in Figure 6.17, for which serial CT sans were available to monitor the change in size of a tumour after an ILP-induced grade I necrosis, and for which almost identical CT sections were available for comparison (bearing in mind that an 8mm slice thickness can give rise to significant error in size estimation of small lesions). Figure 6.18 shows one tumour before, and at various times after ILP, following a grade I necrosis. In 3 patients in whom grade I necrosis occurred in treated lesions, sequential CT scans have demonstrated a gradual reduction and disappearance of these lesions. Figure 6.19 shows the progressive...
resorption of a necrotic lesion and regeneration of normal liver following ILP. Patients in whom a grade II or III necrosis had been achieved invariably had tumour progression within a 2 or 3 month interval, although evidence of treatment-induced necrosis was still seen. It was impractical to try to quantify this progression in size since there was considerable variation between different tumours in their growth rate, and more importantly, interval CT scans of patients with grade II or III tumour necrosis were nearly always taken after a further ILP treatment, which caused more devascularisation of tumour and/or surrounding normal liver and invariably increased the total lesion size (with very irregular margins).

Biopsies of treated avascular areas on CT have confirmed the presence of necrosis and absence of viable tumour in several cases (Figure 6.20). However, a small core of tissue from an 18G Trucut needle cannot be relied on to exclude the presence of tumour in a relatively large volume lesion, even if multiple samples are taken. Also, most of the patients travelled long distances for ILP, and later to have CT and biopsy (requiring admission); logistically, it was far easier for patients to have their CT follow-up assessment locally. Therefore, multiple, frequent biopsies were not routinely performed. In 18 patients and 28 tumours there was documented evidence of necrosis on biopsies taken from corresponding post-ILP avascular areas seen on CT, at various intervals after ILP (2 weeks to 1 year). Biopsies taken from grade I lesions showed necrosis only, with no evidence of tumour, except in 4 cases (tumour size 3cm, 1.7cm, 3.5cm and 3cm); in 3 of these (patients 8, 17 and 23 from Table 6.1), edge recurrence was seen on follow-up CT scans 4-6 months after ILP (Figure 6.21), and in the remaining case (patient 25) tumour recurrence was found on biopsy only, from the edge of the lesion (3 months after ILP). Biopsies from grade II or III lesions confirmed necrosis from avascular areas (6 cases), and residual tumour from the enhancing areas (5 cases). Samples taken from normal looking liver around a previously treated area showed non-specific chronic inflammation (Figure 6.22) up to 5 months post-ILP (in 5 cases).
Figure 6.17: Graph showing changes in size of necrosis with time, after ILP resulting in a grade I necrosis of four tumours, A, B, C and D. The sizes of necrosis plotted at zero months indicates the size of the avascular lesion on CT, 24hrs or 72hrs after ILP. The original size of tumours A, B, C and D (just before ILP) was 17mm, 15mm, 20mm and 30mm, respectively.
Figure 6.18: Series of images before and after ILP of tumour A in Figure 6.17. (a) Liver tumour on ultrasound before ILP, measuring 17mm (+...+). (b) Dynamic CT 24hrs after ILP showing a grade I necrosis (lesion size, 20mm). (c) Dynamic CT six months later showing a reduction in size (10mm) of the necrotic lesion. (d) Ultrasound at six months shows only a small echogenic lesion (arrow).
Figure 6.19: (a) Dynamic liver CT. There is a partially treated metastatic deposit posteriorly. (b) A large area of necrosis and vacuolation is seen after further ILP. (c) & (d) Dynamic CT scans obtained (c) 2 months and (d) 6 months after the final ILP treatment show a gradual resorption and reduction of the necrotic area with replacement by regenerating liver.
Figure 6.20: Liver biopsy taken (a) Before ILP showing adenocarcinoma, and (b) One month after ILP shows coagulative necrosis with no viable malignant cells.
Figure 6.21: (a) Dynamic CT before ILP showing a low density metastasis in the medial segment of the left lobe. (b) 24hrs after ILP, there is complete devascularisation of the tumour, indicating a grade I necrosis. (c) Four months later, dynamic CT demonstrates partially enhancing recurrent tumour on the lateral aspect of the treated area (arrow).
Figure 6.22: Liver biopsy from normal appearing liver on ultrasound, adjacent to a necrotic lesion showing non-specific periportal inflammation (H & E stain, x400).
6.3.4. PATIENT RESPONSE

Eight patients (numbers 1, 8, 22, 23, 25, 26, 27 and 31 from Table 6.1) had all of their tumour destroyed following ILP. Three of these patients (numbers 8, 23 and 25) had tumour recurrence (at the treated site) detected at 4, 6 and 3 months after ILP, respectively. Two of these patients (numbers 8 and 25) were retreated with ILP with no evidence of recurrence at 11 and 12 months following the initial ILP treatment; the third patient (number 23) went on to have systemic chemotherapy. Five (numbers 1, 22, 26, 27 and 31) of the eight patients who had all of their tumour destroyed by ILP remain free from recurrence on CT or biopsy at 17, 10, 10, 7 and 2 months, respectively. However, the CEA level in patient number 1 (Table 6.1) remained elevated after ILP, although it decreased in two of the patients (numbers 22 and 27) in whom it was initially elevated before ILP. Greater than 50% reduction in total liver tumour volume at the end of ILP was found in 24 out of 31 (77%) patients. Because of invariably some tumour progression in grade II and III lesions or new tumours occurring, of those patients followed up for at least 6 months, 17 out of 28 (61%) still had a greater than 50% reduction in liver tumour volume by 6 months after ILP (Table 6.1).

All patients with colorectal metastases who had an initially raised serum CEA had serial levels performed after each ILP treatment; these are given in the appendix. Seven patients had a fall in CEA levels following ILP, although 4 of these patients also had chemotherapy in between CEA measurements. Therefore, only 3 patients (numbers 23, 27 and 29) had a convincing fall in serum CEA following ILP alone. A graphical display of falling levels of CEA after ILP is given in Figure 6.23(a) for four patients (two of which also had chemotherapy around the time of ILP), who had a similar CEA levels before ILP (15-50ng/ml). Nine patients had a rise in CEA, despite a significant reduction in tumour volume; two of these patients (numbers 3 and 12) were later found to have local colon recurrence and pulmonary metastases, respectively. Figure 6.23(b) shows the rise in CEA in four of these patients, graphically. The patient with small bowel carcinoid had a fall in urinary 5-HIAA levels which were related to 3 out of her 8 ILP treatment sessions (Figure 6.24); this patient also reported a general improvement in her main symptom of diarrhoea. All of the other patients treated by ILP had been asymptomatic at the beginning of ILP.

All patients who had a grade II or III necrosis of some or all of their tumour deposits, showed evidence of disease progression on follow-up. All of these patients had some increased growth of residual tumour or new liver metastases (12 patients) separate from the treated sites; the extent and rate of progression was variable and dependent on the length of follow-up. Four patients (numbers 4, 9, 12 and 24) developed pulmonary metastases after ILP at 22, 15, 9 and 8 months follow-up, respectively. Three patients (numbers 3, 17 and 24) were found to have non-pulmonary extrahepatic tumour recurrence after ILP at 8, 8 and 12 months follow-up, respectively; all three also had increased liver tumour, with
increased growth around previously treated tumours, as well as new intra-hepatic tumours (numbers 17 and 24).

6.3.5. COMPLICATIONS

ILP treatment was well tolerated by most of the patients, regardless of the number of tumours treated. Mild abdominal discomfort during treatment and for 24 to 48 hours afterwards was common. Additional analgesia was often required for lesions adjacent to the liver capsule, either for shoulder pain due to diaphragmatic irritation or abdominal/back pain probably due to heat conduction to nearby peritoneum or retroperitoneum. In 5 cases (2 tumours adjacent to the diaphragm, and 3 next to the peritoneum) the pain resulted in shortening of the treatment time with intermittent bouts of 100-300s, rather than continuous 500s; the treatment was, however, completed in all 5 cases. A marked bradycardia occurred in one patient during treatment of a lesion in the tip of the left lobe, and was thought to be due to stimulation of vagal branches in the adjacent stomach wall. Three patients had a prolonged hypotensive episode associated with a mild bradycardia (systolic blood pressure 60-80mmHg for 5-15 minutes; these patients responded to a combination of intravenous fluids and atropine. Another 3 patients had significant hypertension during and after ILP treatment (blood pressure 180/110 to 240/140mmHg for up to 1 hour); these patients were all well sedated and pain free, and the blood pressure gradually returned to normal over 1-2 hours following ILP. One of these patients had subsequent ILP under general anaesthesia during which the blood pressure remained well controlled. All other patients were haemodynamically stable in the 24hrs post-ILP, but the subsequent CT scan did demonstrate small subcapsular haematomas in 6 cases, and in one case there was a drop in haemoglobin by 2g/dl after 2 treatments 1 week apart. A rise in serum transaminases occurred in most of the patients following ILP, except when there was limited treatment to a small tumour volume. At 24 hrs post-ILP this rise varied from 1.5 to 8 times the pre-ILP levels, but always returned to normal by 3 to 14 days. This would be consistent with a transient inflammatory response in the liver adjacent to the treated areas, especially if 2 or 3 metastases were treated in one session. Small pleural effusions were seen on post-ILP CT scans in 10 cases after treating lesions close to the diaphragm, but there were no respiratory symptoms and the effusions had resolved by the time of the following treatment session. All patients were discharged by 24hrs post-ILP, and all were given morphine elixir for a few days, with non-steroidal anti-inflammatories, to be taken as needed; most patients required some oral analgesics for 24-48 hours after ILP, although on 12 occasions patients required opiate analgesia for up to 10 days. A transient and mild elevation of temperature with malaise was reported in several cases 24-72hrs post treatment, which was probably due to an inflammatory response to the presence of necrotic tissue in the liver. Five patients developed cystic collections at the treatment site (Figure 6.10); one of these patients was asymptomatic and the cystic area had resolved by 2 months; two patients had asymptomatic but persistent collections at 11 and 17 months follow-up. The other 2
patients had had superficial tumours treated and the cystic collections partly communicated with the anterior abdominal wall; both of these patients had persistent local pain and intermittent fever for 2-3 weeks after ILP. One patient responded to a course of antibiotics and analgesics, but the other patient required aspiration of some fluid (not found to be infected) which resulted in improvement of symptoms and resolution of the cystic collection.

One patient was found to have dilated left biliary ducts 1 month after ILP to a tumour lying just anterior to the porta. This has persisted on follow-up 6 months later, but the patient remains asymptomatic and has a normal serum bilirubin level. Another patient developed a 3cm thrombus in the inferior vena cava, below the renal veins, and well away from any treated hepatic tumour; this patient was also asymptomatic and the thrombus not thought to be related to the ILP treatment.

6.3.6. SURVIVAL ANALYSIS

Of the 31 patients treated with ILP over the past 4 years, 9 have died (median survival after ILP was 16 months, range 4-40 months) and 22 are still alive (median follow-up 12 months, range 2-37 months). A life table analysis of this data is given in Table 6.5; this needs to be interpreted with caution, since the numbers are small, follow-up time is short, and many patients also received some form of chemotherapy.

Table 6.5: Life table analysis using the Kaplan-Meier method of estimating survival times after ILP. (Data from Table 6.1).

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The corresponding life survival curve is shown in Figure 6.25. From this, the estimated one year survival of patients following ILP was 85%, two year survival 76%, and three year survival 38%.
Figure 6.23: (a) Graph showing fall in serum CEA after ILP in four patients whose initial CEA level just prior to their first ILP (at zero months on graph) was in a similar range. The dotted curve represents those patients who had chemotherapy around the time of ILP, which may also have had an influence on the serum CEA level. Normal CEA is 0-5ng/ml. (b) Graph showing rising serum CEA after ILP in four patients whose CEA levels were in a similar range. Each patient had their first ILP treatment at zero months. The times of further ILP treatments to the patients in (a) and (b) are indicated in the appendix (pages 211 and 212).
Figure 6.24: Graph showing change in 24hr urinary 5-HIAA levels in the patient with carcinoid following each ILP treatment (represented by a square). The urine collections were made just prior to each of the treatment sessions. The final reading (represented by a cross) is a follow-up reading only (ie. no treatment at this time). Normal urinary 5-HIAA is less than 45mmol/24hrs.

Figure 6.25: Life survival curve of patients after ILP to their liver metastases (Kaplan-Meier life table analysis). All of the black dots (except the first, at 0 months) represent the time of a patients' death. The longest survivor died 40 months after ILP, but no patient has so far been followed up for longer than this time.
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<th>Size (cm)</th>
<th>Total no. of laser treatments</th>
<th>Necrosis grade at end of ILP</th>
<th>Survival since start of ILP (months)</th>
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<td>4</td>
<td>3.0</td>
<td>1.5</td>
<td>I</td>
<td>7</td>
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<td>29 M</td>
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<td>7</td>
<td>3.0</td>
<td>2.0</td>
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<td>4</td>
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<td>2</td>
<td>alive</td>
<td>yes</td>
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* indicates that all of liver tumour destroyed, and currently there is no detectable viable tumour.
† indicates those patients who had a greater than 50% reduction in tumour volume at 6 months after the end of their ILP treatment.
6.4. DISCUSSION

6.4.1. ILP TECHNIQUE

This study shows evidence of laser induced tumour necrosis in all 93 liver metastases treated by ILP. Greater than 50% reduction in tumour volume (grade I or II) was achieved in 89% of tumours treated, and in 77% of patients. This response compares favourably with other palliative, non-surgical methods of treating liver metastases which can have significant morbidity and no convincing survival benefits (Taylor, 1985). Regional intra-arterial chemotherapy for liver metastases produces a significant response (defined as 50% or greater reduction in tumour volume) in 40-60% of patients, but given systemically the response rate is only 10-21% (Ensminger, 1993). Unlike chemotherapy, all tumours treated with ILP show some response, although if chemotherapy is effective it should have a more global effect on micro-metastatic and extrahepatic disease when given systemically. New techniques for local destruction of liver tumours include cryotherapy and percutaneous injection of alcohol; cryotherapy requires a laparotomy, and alcohol injection is relatively ineffective for liver metastases (Amin et al, 1993). Radiofrequency electrocautery is a promising new percutaneous method of thermally destroying liver tumours, but clinical experience is currently very limited.

The principles and applications of ILP are fairly simple. Lasers are becoming more widely available in hospitals, and if one is already installed for other uses (such as endoscopic high power therapy for obstructing oesophageal and rectal carcinomas), it is relatively easy to extend its use for ILP if an appropriate beam splitter (coupler) is acquired and there is support from a radiologist and physicist. The beam splitter is the limiting factor with respect to the maximum output power per fibre - currently 2W per fibre is the upper limit before the coupler overheats and becomes permanently damaged. The careful construction and alignment of the input fibre from the coupler to the output beam of the laser is crucial, and adequate time must be spent on this (preferably by a physicist) to avoid malfunction and “burn-out” of the connector during a clinical ILP session.

Although experimentally, using a 4 fibre system, a 3-4cm diameter area of necrosis is consistently obtained in normal liver (Steger et al, 1992), 29% of tumours measuring less than 4cm (ie. 21 out of 72, Table 6.4) failed to show 100% avascularity (grade I necrosis) on post-ILP CT. The most likely explanation is difficulty in accurate needle-tip placement. There is a much higher chance of achieving a grade I necrosis, and include a margin of normal liver, when placing 4 needles into a small tumour with a diameter of 2cm or less, than placing 4 needles into a 3-4cm diameter tumour. Accurate targeting becomes far more crucial for the larger tumours, and this is the main factor limiting the extent of necrosis achieved. Other possible reasons include: problems with tumour accessibility; poor patient tolerance, resulting in shortened treatment times; different absorption characteristics

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of laser light by the tumour compared with normal liver. Tumours are heterogeneous lesions with a variable blood supply, as opposed to relatively homogeneous normal liver. Absorption of laser light is dependent on the presence of blood in tissue (Jacques et al., 1992) and hence on the vascularity of the tumour, and it may also depend on the type of tumour; in addition, the temperatures reached around the fibre-tip will depend on the local circulation and cooling by flowing blood. Thus, the laser parameters which give a well-defined and reproducible lesion in normal liver may result in a non-uniform and less predictable lesion in tumours. Because of these factors, it is not practical to have a fixed deposition of laser energy for any given tumour size; ILP to tumours of the same size may result in different necrosis extent, despite using the same amount of laser energy.

The problem of accurate targeting of tumours is highlighted by the fact that four grade I necrotic lesions had tumour recurrence at their edges (two of these measured 3cm, one 1.7cm and one 3.5cm). Although ideally, a margin of normal liver around the tumour should also be necrosed, this was not always achieved because of the factors discussed above.

The number of treatments performed per metastasis in this series was very variable. This is due to the factors outlined above as well as limitations of procedure time and the need to treat more than one deposit during the same session, in some patients. Often, with more extensive disease in some of our earlier patients, the intention was to significantly debulk tumour rather than completely eradicate it, and so time was better spent treating several lesions rather than trying to achieve 100% necrosis of a single lesion. However, patients are now selected with smaller tumours (ie. less than 4cm), and the intention is to completely ablate the tumour.

6.4.2. IMAGING

Imaging plays a crucial role in ILP. Its initial function is the reliable detection of the number, location and sizes of liver tumours, so that the treatment can be adequately planned. The success of ILP is dependent on accurately delivering the needles/optical fibres to the target area, monitoring the effects of the treatment in real-time, and subsequently evaluating the extent of thermal damage. The key to achieving these objectives is in the imaging methods used.

In this study, CT (non-contrast, dynamic and delayed) was the main modality for tumour detection. Dynamic CT was the most sensitive technique for tumour detection, since the majority of the tumours were hypovascular. The dynamic CT technique was, however, suboptimal because of the relatively slow liver scanning time of 5-6 minutes. It is well established that the peak liver-to-tumour contrast occurs within the first 2-3 minutes following a bolus intravenous injection of contrast medium; after this time, contrast
medium enters the interstitial spaces of the tumour, making it less conspicuous in the surrounding liver parenchyma. During dynamic CT of the liver in this study, lesion to liver contrast was maximal during earlier scanning of the cephalad half of the liver, but decreased appreciably when scanning was continued in the later caudad sections (after 2-3 minutes). However, the overall sensitivity of liver tumour detection was increased by performing delayed CT scans, as well as ultrasound scanning just prior to ILP.

Ultrasound has a useful role in ILP of liver tumours. It can be used to confirm the pre-treatment CT findings and may allow detection of further lesions not seen with CT, although lesions seen on CT may sometimes not be visible on ultrasound. In experienced hands ultrasound allows accurate needle-tip positioning into the desired sites within the tumour. Real-time imaging of the treated area as a developing and enlarging echogenic zone was reliable in predicting the extent of necrosis in the treatment of smaller (less than 3cm) metastases. Difficulties arose in the treatment of larger lesions due to degradation of the ultrasound image by echogenic material, and subsequent problems in clearly identifying remaining tumour as well as in seeing the needle tips with ultrasound. This could result in areas of tumour escaping treatment; however, the presence of echogenic changes does provide an indicator that thermal damage is occurring. Ultrasound is also unhelpful in the evaluation of lesions after treatment, since ILP produces well-defined, solid areas of coagulative necrosis with ultrasound characteristics fairly similar to those of tumour tissue. This similarity in ultrasound appearance between treated and untreated tumour made subsequent targeting of the residual tumour difficult, and was the main reason why it was rarely possible to progress from a grade II or III necrosis to a grade I necrosis despite several treatments.

CT can be used to localise tumours not seen on ultrasound, but it is of limited value for evaluating the extent of ILP-induced necrosis during and immediately after treatment. Twenty four hours or more later dynamic CT shows the results of ILP very clearly as well-defined, non-enhancing areas, which are easily distinguished from untreated enhancing tumour. The optimal time to perform the post-ILP CT assessment was found to be after 1 to 4 days, which corresponds well with the time at which an experimentally induced necrotic lesion has its maximum size (Mathewson et al, 1987). Maximal lesion to liver contrast on CT occurs 2-3 minutes after intravenous contrast (Young et al, 1980), and most hypovascular non-necrotic lesions gradually become iso-dense after this time. However, necrotic lesions are likely to take much longer to become iso-dense (Walkey, 1991), which is why the scan time of 5-6 minutes used in this study still gives very good lesion-to-liver contrast. Dynamic CT scans were more useful than pre-contrast or delayed scans in evaluating treatment-induced necrosis. Delayed CT scans were performed prior to ILP because some hypervascular tumours become iso-attenuating to normal liver during dynamic contrast enhanced scanning (Bressler et al, 1987), and this was seen in 2 patients who had liver secondaries from a pancreatic islet cell tumour and a small bowel carcinoid.
The enhancing rim which sometimes appeared around a grade I necrotic lesion between 1 and 4 weeks post-ILP (Figure 6.14) can pose a problem because CT cannot differentiate between inflammatory change, regenerating liver, or recurrent tumour. Histologic specimens from this rim exhibited inflammatory change in one case and recurrent tumour in another case. The enhancing rim should be viewed with suspicion of possible tumour recurrence, especially in tumours which are 3cm or larger before ILP. In these cases it would be prudent to repeat CT scans 3-4 weeks after ILP, and if an enhancing rim is found, guided biopsies of this area should be undertaken. Otherwise, CT at 24hr or 72hr after ILP gives adequate information about the extent of necrosis, and is a convenient time to perform the scan.

The MRI sequences used in the small group of patients did not give any further clinically useful information, compared to dynamic CT, for the evaluation of laser-induced necrosis after ILP. T2 weighted images showed the necrosis more clearly than T1 weighted images, but gadolinium enhanced rapid T1 weighted images gave the best definition of the boundaries of necrosis. However, dynamic CT gave similar, if not better images, and more importantly, untreated tumour could be seen on dynamic CT. The liver metastases were poorly seen on the pre-treatment MR scans, and so differentiating treated from untreated tumour is clearly a problem if the former is not imaged well. Dynamic CT is also much easier to perform, since rapid MR imaging requires accurate localisation of the region of interest prior to administering contrast (which can be difficult), and the latter also only allows a few cuts to be taken in a similar phase of contrast enhancement during a single breath hold (since only 10mls of gadolinium is used for MRI).

6.4.3. EVALUATION OF RESPONSE TO ILP

Grade I tumour necrosis (indicated by 100% avascularity on CT) was achieved by encompassing the whole tumour by an echogenic zone on ultrasound as well as a margin of surrounding normal tissue of about 1cm thickness in order to destroy any undetected extension of tumour. A grade I necrosis implies an assumption that the avascularity (or non-enhancement) on CT is indicative of necrosis with non-viable tumour. Although this can only be proven with detailed histological correlation, it is a logical assumption for 3 reasons. Firstly, several biopsy specimens from post-ILP avascular parts of a lesion have confirmed necrosis; secondly, experimental work on normal liver, using the same laser parameters, shows a well-defined area of coagulative necrosis which corresponds with arteriographic findings of obliteration of all small vessels and luminal narrowing and occlusion of some larger vessels in the treated area (Matthewson et al, 1987; Steger et al, 1992). Thirdly, the temperatures reached at the fibre tip are over 100°C, and 8mm away are over 50°C (Matthewson et al, 1987), making it highly unlikely that tumour cells can survive these temperatures for the treatment time of 500s. Takayasu et al (1984) correlated CT images of liver tumours treated with chemo-embolization with pathological specimens
after surgical resection, and found non-enhancing areas to correspond well with treatment-induced necrosis.

Healing of the necrotic lesion is by fibrosis and regeneration, and a 3cm lesion in normal rat liver takes up to 1 year for resorption of necrotic tissue and regeneration of normal liver to be complete (Matthewson et al, 1987). This is consistent with the clinical findings in this study, with the slow disappearance of three grade I lesions.

Ultrasound guided liver biopsies using 18G Trucut needles do confirm necrosis in selected areas which have been treated with ILP. However, this is not a reliable way of evaluating complete tumour necrosis because even multiple biopsies will only give information on a very limited volume of liver and accurate sampling from a specific area seen on CT, such as an enhancing rim, is not easy to perform. Since the ILP treatment can easily require more than 12 needle passes, there is a theoretical risk that undertaking additional multiple 18G Trucut biopsies may cause significant haemorrhage. CT-guided biopsies may be of use in sampling enhancing margins, although to localise the needle tip within fairly narrow rims of tissue may present problems. The histological finding of a “fixed” zone of non-viable cells which appear morphologically normal on H & E staining, means that there may be a significant risk of false positives from core biopsies unless formal histochemical staining is performed. The only way of confirming absence of viable tumour is to resect the lesion post-treatment, but this is unlikely to be a practical or feasible option in most patients.

Monitoring of the biological marker, CEA, in patients with colorectal liver metastases showed an ILP treatment related decrease in only 3 patients (a further 4 patients had a decrease in CEA following ILP and chemotherapy). Nine patients had a clear rise in serum CEA after ILP despite a significant reduction in tumour volume. All of these patients had a Dukes C colorectal carcinoma at the time of resection of their primary tumour, and most patients had significant tumour volume when referred for ILP. Although CT scans of the abdomen and pelvis and a chest X-ray showed no obvious extra-hepatic disease at the onset of ILP, it is likely in patients with a Dukes C carcinoma (two patients were later found to have extra-hepatic disease on CT scanning). In one of the patients (number 1 from Table 6.1) who had complete tumour avascularisation of his single liver metastasis achieved on CT criteria, the CEA rose after ILP treatment. Treating some lesions was invariably associated with progression of others during the treatment interval. These factors may account for the continued rise in CEA seen in many of the patients. What is needed is careful monitoring of patients who have surgically resectable disease in whom ILP is performed because they are either unfit for surgery or refuse an operation. The patient with carcinoid did show a reduction in urinary 5-HIAA related to 3 of the ILP treatment sessions and associated with an improvement of symptoms. The fact that there was a rise in 5-HIAA levels following 4 of the treatments may be related to which of the metastatic deposits was treated; only those carcinoid deposits which secrete 5-HIAA directly into the
systemic circulation (via the hepatic venous system) contribute to the urinary levels (Beaton et al, 1981). Hence, one can postulate that only by treating these deposits will there be a fall in urinary 5-HIAA.

All except one of the patients treated were asymptomatic from their liver tumour, therefore no subjective patient parameter could be assessed. Indeed, ILP converted asymptomatic patients to temporarily symptomatic ones, although overall morbidity was low with good patient tolerance. This is especially important since it is unproven whether ILP extends the duration of good quality life.

When evaluating the response to ILP, it should be remembered that most patients also received some form of chemotherapy, which may have prevented any local recurrence in grade I lesions, and so biased the follow-up results favourably.

Although in this study and in most other studies evaluating response to tumour therapy, “partial” and “complete” responses are quoted, many clinicians feel that partial responses are of dubious benefit, and only complete responses should be quoted as they are more likely, if at all, to influence patient outcome, in trials of unproven treatments (Watson, 1981). The other major problem with partial responses are the way they are assessed - it is generally agreed that they represent a greater than 50% decrease in measurable lesions, but the measurements quoted may be diameters, areas or volumes of tumours. This is clearly of importance since a 50% decrease in diameter results in a 75% decrease in area and a 87.5% decrease in volume. The UICC (International Union Against Cancer) recommendation is based on the product of 2 diameters, and is equivalent to an area assessment. In this study, volume assessments have been used since the necrotic lesions were often very irregular, and sometimes varied dramatically from one plane of imaging to another; therefore, measurements based on 2 diameters alone are likely to have resulted in significant errors. The irregularity of the necrotic lesion did however, mean that errors in estimating volumes were inevitable (Fomage, 1993), a problem exaggerated in the liver because of respiratory variation and overlap of some scan slices. This indicates that the grade II or III data should be interpreted with some caution, and that the grade I data gives a more valid assessment of tumour response.

6.4.4. SAFETY OF ILP

Overall, the complication rate in the patients treated by ILP was low, and the treatment itself was generally acceptable to patients, who were all kept in hospital for only one night after ILP. Significant problems with bleeding were not encountered and there were no biliary leaks, despite up to twelve 18-19G needles inserted into the liver, often close to the hilum, as well as 18G Trucut biopsies being frequently taken. The most significant complication was a presumed stricture of the left main hepatic bile duct resulting in biliary tract dilatation
in the left lobe of the liver. This was likely to have been a result of the ILP treatment rather than tumour overgrowth, since it occurred soon after ILP and there was no obvious evidence of tumour recurrence on the liver CT scan; the patient remains asymptomatic with no progression of biliary dilatation 6 months later. However, this emphasises the need for caution when applying ILP close to the porta, even though there may be some protection of the main biliary radicals by flowing blood (conducting heat away) in adjacent portal veins. The elevated blood pressure in some patients during ILP, despite the absence of pain or obviously excessive anxiety (patients well sedated, without a tachycardia), may still have been due to the general stress of having ILP treatment, especially since this was not a problem in one of the patients during ILP under a general anaesthetic. The prolonged hypotension in three patients may have been due to a prolonged vasovagal attack; other possible explanations include drugs (pethidine and diazepam), transient bacteraemia, and release of toxins from the dead tissue. Although these patients all responded to intravenous fluids and atropine, one must be aware of the risks of myocardial infarction or a cerebrovascular event, especially in elderly patients or those with underlying ischaemic heart disease.

The most common and troublesome side effect of ILP was local or shoulder-tip pain during and after ILP. This invariably occurred in tumours close to the diaphragm or peritoneum. In the latter case it was difficult to avoid heating the peritoneum since this occurs during pulling back of the needles/fibre-tips, in order to destroy more proximal tumour; when this is done, it is very difficult to know the exact location of the needle-tips because of the degraded echogenic field of view from the earlier treatment. Hence, there is a risk of heating part of the abdominal wall as well as liver capsule and peritoneum. Of course, if the tumour lies adjacent to the liver capsule, the only way to destroy its most superficial aspect is to heat the overlying capsule and peritoneum, and inevitably part of the abdominal wall.

Although there is a theoretical risk of infection this is reduced with antibiotic cover, and there were no obvious hepatic abscesses in the patients treated in this study. Other potential complications include biliary fistulae and haemobilia, but these have not so far occurred. There is an argument for avoiding extensive laser-induced tumour necrosis during ILP because of the theoretical risk of acute tumour lysis syndrome (Chasty and Liu-Yin, 1993); this results from a rapid massive release of cellular breakdown products consequent upon tumour cell death following effective therapy. Normal excretory mechanisms may become overwhelmed, resulting in metabolic disturbance (such as hyperkalaemia, hyperuricaemia, hyperphosphataemia, and hypocalcaemia) which can lead to sudden death or prolonged morbidity from renal impairment. Another potential concern is tumour spread by the technique itself; seedling from needle puncture is however minimised by the fact that the deepest margin of the tumour is treated first, followed by more proximal tumour as the
needle/fibre-tip is withdrawn, until the most proximal margin of the tumour is destroyed prior to withdrawing the needles.

From this study and the currently available data, it can be concluded that ILP is a relatively safe technique for destroying liver tumours, with a low morbidity.

6.4.5. **PATIENT SURVIVAL**

The survival analysis undertaken in this study is limited by the small number of patients and relatively short follow-up time. Furthermore, most patients received some form of chemotherapy, which may have influenced patient survival. Of the 31 patients, 26 had colorectal liver metastases; 7 of these patients have died (median survival 27 months, range 9-40 months) and 19 are still alive (median follow up 11 months, range 2-37 months). Life table analysis just on these 26 patients with colorectal liver metastases gave a 1, 2 and 3 year estimated survival of 91%, 81% and 24%, respectively. These clearly need to be interpreted with caution because of the very early nature of this analysis, making the 3 year figure of 24% particularly unreliable. An estimation of their percentage hepatic replacement by tumour varied from less than 1% to 24%. Inspection of the natural history data for colorectal liver metastases (Table 1.3) shows that for tumour volumes of less than 25%, untreated patients have a mean survival of 6.2 months (Bengtsson et al, 1981); the 1 year survival varies from 6% (widespread tumour) to 85% (less than 4 metastases) depending on the extent of hepatic tumour, and the 3 year survival varies from 4% to 26%. Following surgical resection of colorectal liver metastases (Table 1.4), the median survival is 22-36 months, and the 1 year and 3 year is 70-92% and 40-73%, respectively.

No valid comparisons can however be made, between the results of ILP and the survival of untreated patients or of those following surgery. This is because of the problems discussed above. Simply grouping together patients with less than 25% PHR is inadequate, since patients with less than 5% PHR are likely to survive significantly longer than patients with 20-25% PHR. Also, there is bound to be considerable variation in the tumour biology and aggressiveness between patients with similar tumour volume loads.

It may be reasonable to cautiously suggest that the survival of these patients appears promising, and it is unlikely that ILP is doing any long-term harm to these patients. There are certainly theoretical grounds for thinking that if liver metastases can be completely destroyed *in situ* by ILP, then patient survival may improve.

The only way to answer the question of survival benefit is to perform a prospective, randomised controlled trial with careful stratification of similar patients with similar tumour volumes into the comparative groups. It is unlikely to be acceptable to patients to have no
treatment offered in such a trial, and so ILP needs to be compared with another modality, such as chemotherapy, or another local therapy.

6.4.6. CONCLUSIONS

This study has shown that percutaneous ILP can effectively destroy most liver metastases measuring 2cm or less in diameter, using 8 needles and including a margin of surrounding normal liver. This can be done safely with minimal morbidity; ILP also has the advantage of being easily repeated many times in any one patient. However, like most other local therapies, ILP is non-specific and will destroy normal tissue as well as tumour. For tumours of 3cm diameter or larger, accurate targeting is a major problem, and at least a small part of the tumour margin is likely to be missed, making recurrence very likely. Imaging plays a vital role in ILP, but there is a need for improvement, particularly with more accurate targeting, as well as real-time monitoring of thermal changes. Ultrasound and dynamic CT are currently the best modalities available - ultrasound being used for targeting tumours and allowing some real-time thermal tissue changes to be seen, and dynamic CT 1-4 days after ILP shows treated and untreated areas and can be used for treatment evaluation and planning.

Recruitment of patients for ILP treatment should be aimed at those patients with small volume tumour which can be potentially completely destroyed by ILP; for example, patients should have no more than 4-5 liver metastases, which should be no larger than 2-3cm. With improvements in ILP, it may become feasible to treat larger tumours. However, since it is unknown whether even complete liver tumour destruction by ILP improves patient survival, there is no argument yet for routine debulking of liver tumour in patients with colorectal liver metastases. Debulking by ILP can reasonably be offered to patients with symptomatic endocrine tumours, since other palliative debulking treatments have been shown to be beneficial. In such patients, one should avoid treating those tumours (especially superficial ones) which may potentially cause more symptoms (such as prolonged pain) than were present before treatment, until a clear benefit in survival terms is seen.

With further development of the technique, and after proven benefit following randomised controlled trials, ILP has the potential of becoming a realistic alternative to surgery in selected patients, but, more importantly, it may offer some benefit to the large number of patients with limited tumour volume in whom surgery is inappropriate.
SECTION D: CONCLUSION

CHAPTER 7: SUMMARY AND FUTURE DIRECTIONS

7.1. Summary of Thesis

7.2. Future of ILP
   7.2.1. Laser parameters and fibre-tips
   7.2.2. Imaging
   7.2.3. Clinical work
This thesis assesses a relatively new technique of liver tumour destruction, called interstitial laser photocoagulation (ILP), in which the tumours are heated by direct delivery of low power laser energy via optical fibres inserted percutaneously through thin hollow metal needles. Experimental and clinical work was performed and evaluated with the overall objective of safely and effectively destroying human liver tumours. The aims of the experimental work were: (a) to clarify the mechanism of action of ILP, (b) to improve the laser parameters used for ILP, so that the extent of thermal damage can safely be increased and isolated liver tumours completely destroyed, and (c) to accurately assess the extent of thermal damage histologically and radiologically. The aim of the clinical work was, (d) to perform a detailed evaluation of the clinical application of ILP by continuing to treat patients who have small volume liver metastases.

Section A is the background to the thesis and consists of chapters 1-3. Chapter 1 first sets out the scale of the problem, with the large number of patients developing liver metastases for whom there is currently little effective therapy. It then describes the current methods of detecting liver metastases using biochemical tests and imaging, and outlines the limitations of the current imaging modalities for tumour detection. The natural history of liver metastases is described in detail, in order to emphasise the fact that some patients with small volume liver tumour may survive for several years without any treatment. The final part of chapter 1 deals with the treatment options available for patients with liver metastases, the main ones being surgery and chemotherapy. Regional and local treatments of liver metastases are then described, and a comment made about the importance of treating patients with liver metastases in the setting of a controlled clinical trial.

Chapter 2 describes the local treatment for liver tumours which forms the subject of this thesis, namely ILP. The principles of ILP and laser-tissue interaction are explained, and then a critical review of the experimental and clinical literature on ILP given.

Chapter 3 highlights the current deficiencies in the knowledge of ILP, and summarises the aims of the thesis.

Section B is the experimental section of the thesis and consists of two chapters, 4 and 5. Chapter 4 consists of six separate studies involving ILP to 108 Wistar rats and 2 Large White pigs. These studies investigated the effects of different fibre-tip modifications and laser wavelengths on the size of necrosis produced after ILP to the animal liver. The most significant finding was that tissue charring around the optical fibre-tip was associated with greater necrosis, which was contrary to the previously held belief that charring is disadvantageous during ILP. The cladding material around an optical fibre
was also found to be very relevant, plastic clad fibres giving greater necrosis than silica clad fibres, due to greater char formation with the former. Another important finding was that less penetrating wavelengths such as the 1320nm Nd:YAG and 805nm diode produced greater necrosis than the more penetrating 1064nm Nd:YAG wavelength, again contrary to previously held views. This difference was essentially due to the greater char formation around the fibre-tip when less penetrating wavelengths are used for ILP, since the temperatures in the vicinity of the fibre-tip are much greater when all of the energy is focused into a smaller volume. This led to the “hot-tip” concept of ILP, which was extended experimentally by pre-charring the fibre-tip and by attaching metal needles to the tip; in both cases the necrosis was greater than that produced by a clean silica clad fibre-tip with a 1064nm Nd:YAG laser. The study in pig liver involved heating the distal part of a long metal needle, by placing the fibre-tip 1-3cm proximal to the needle-tip; however, significant problems arose with burning of the fibre cladding at powers of 4W and 8W, resulting in irregular and unpredictable necrotic lesions. An interesting pathological finding was observed in the pig liver experiments, that of vascular thrombosis and perivascular necrosis around small vessels projecting for distances of up to 10mm away from the main necrotic lesion; this was thought to be due to passage of steam bubbles along these vessels.

Chapter 5 consists of two experiments, involving a total of 48 rats. The first was a study describing the histological features of charred and uncharred necrotic lesions in rat liver 24hrs after ILP, and determining the extent of necrosis by standard H & E staining as well as histochemical staining for a mitochondrial enzyme, diaphorase; temporal histological changes were also evaluated, at various times after ILP. The typical microscopic features consisted of a targetoid lesion with six distinct concentric zones, and the main finding of interest was that of a broad zone of “preserved” hepatocytes within the necrotic lesion, outside which (where the temperature was lower) was a zone of active necrosis; the diaphorase staining clearly showed that these apparently “fixed” cells were not viable. This zone was probably due to heat-fixation, and was present for at least three weeks after ILP. The second part of this chapter was a CT-pathologic correlative study of ILP in 24 rats, at 24hrs and 2 weeks after ILP, the plane of imaging and sectioning of the rat liver lobe clearly defined by radio-opaque markers attached to the liver lobe. This confirmed that the extent of tissue density change on CT corresponded to the extent of necrosis pathologically, and that the optimal CT technique for imaging ILP-induced necrosis was dynamic contrast-enhanced scanning.

Section C consists of chapter 6, which describes the clinical application of ILP to treat patients with liver metastases (mostly from colorectal primaries). A total of 93 tumours in 31 patients were treated by ILP, and imaging performed with ultrasound and CT in all patients, as well as MRI in 6 patients. Ultrasound showed the thermal changes during ILP as an expanding echogenic zone around the fibre-tips, but the margins were usually
irregular and the exact extent of thermal damage was not reliably shown. Dynamic CT clearly showed ILP-induced necrosis as a new area of non-enhancement, untreated tumour continuing to partially enhance. The best time to perform CT assessment was 24hrs or more after ILP. Gadolinium enhanced MRI, using rapid T1 weighted sequences showed the effects of ILP as a well-defined non-enhancing area but did not give any more information than dynamic CT in the six patients imaged. Necrosis of tumour volume was more than 50% in 89% (83 of 93) of the tumours, and 100% necrosis was achieved in 55% (51 of 93). Tumours smaller than 4cm were treated more effectively than larger tumours; no tumour greater than 3.5cm was destroyed completely, but 75% of tumours 2cm or less in size were completely destroyed. Eight patients had all of their detectable tumour destroyed by ILP, and five of these patients remain free from recurrence at 2-17 months follow-up. Of those tumours completely destroyed, edge recurrence was detected in four (sizes 1.7cm, 3cm, 3cm and 3.5cm). Serum CEA levels fell in 7 patients after ILP (4 also had chemotherapy), but continued to rise in 9 patients. Complications were minor, and included pain, transient fever, hypo- and hypertension, asymptomatic pleural effusions and subcapsular haematomas, and cystic collections at the treatment site. The most significant complication was dilatation of the left sided biliary ducts after ILP to a tumour close to the porta, although the patient remained asymptomatic with a normal bilirubin. A survival analysis was performed, although it was emphasised that the patient numbers were small, follow-up relatively short, and many patients also received chemotherapy.

7.2. FUTURE OF ILP

For ILP to become clinically acceptable, improvements need to be made in the technique so that larger tissue volumes can be safely and effectively destroyed; improvements are also needed in the imaging methods used, particularly with more accurate targeting and real-time monitoring of ILP. Clinical experience also needs to be increased, preferably within well-structured and controlled trials. These aspects of ILP are discussed below.

7.2.1. LASER PARAMETERS AND FIBRE-TIPS

There is considerable scope for improving the laser parameters and achieving greater necrosis safely. Several ways of achieving greater necrosis have been highlighted in this thesis. With the current state of knowledge, and the fact that the most widely used laser is the 1064nm Nd:YAG, it is presently appropriate to use sterile plastic clad fibres with this laser, for ILP, although one must take more care with these compared to silica clad fibres since they are less resilient. The main drawbacks of most Nd:YAG laser units are their large size, limited portability, and frequent requirement of fixed installation for water cooling and three phase power supply; in addition, these systems are relatively
expensive, making the possible widespread adoption of laser technology slow. However, the future lies in semiconductor lasers since they are small, compact, portable, easy to use, and do not require any special water cooling or three-phase electricity supply; they have a relatively high electrical to optical conversion efficiency, the heat generation is low, and the unit is therefore cooled by convection (air cooled), which means that the laser is also silent during operation. These diode laser units also have a potentially longer operating lifetime, and require virtually no routine maintenance. The maximum power output of these lasers is currently 25W, which is more than enough for ILP, but inadequate for high power endoscopic tumour vaporisation, the latter being a common reason for having a laser installed in a hospital. For economic reasons, it is preferable to have a laser which can be used for several medical applications. It is envisaged that higher power (0-75W) diode lasers will become available in the next 1-2 years, and it is likely that they will then be widely used. Although the 25W diode laser presently available currently costs about the same as a Nd:YAG laser, the price is likely to be substantially less in the future. The 805nm wavelength of the diode laser makes it particularly suitable for ILP, since this consistently produces larger necrotic lesions than the 1064nm wavelength, as shown in chapter 4. The patients treated so far have had ILP performed by using a 1x4 beam splitter, allowing activation of four optical fibres simultaneously. Development of a 1x8 or a 1x12 coupler which can give a stable output of 2W per fibre and be usable with the diode laser will help to increase the extent of necrosis produced from a single 500s exposure, and considerably reduce the treatment time.

This thesis has shown that a point heat source gives larger necrotic lesions than a distributed optical source during ILP, and so the ideal fibre-tip is one which focuses all of the laser energy immediately around the tip. Diffuser tips which are designed to avoid charring tend to be relatively large and produce much less necrosis than bare fibre-tips. One exception to this is the diffuser tip used experimentally and clinically by Nolsoe et al (1992 and 1993), which is long and thin (tapering distally), and allows higher powers to be used, creating necrosis with central charring. This type of fibre produces cylindrical necrosis with the length of necrosis defined by the length of the fibre-tip. Development of thin metal needle-tips, which can be firmly attached to the end of a fibre and which do not stick to charred tissue, would also allow controlled cylindrical lesions to be produced. If the length of necrosis could be made to be entirely dependent on the length of the needle/fibre-tip being used, then the width of necrosis may be increased by increasing the laser power (above 2-3W) and energy delivered down the fibre. Activating several such fibres simultaneously could produce much greater necrosis than is achieved with bare fibre-tips, although a beam splitter which can tolerate the higher powers would be required.
With the hot-tip concept of ILP now established as being desirable, the potential role of other modalities which can produce hot-tips needs to be evaluated for treating liver tumours. The main alternative to lasers is RF electrocautery, which allows a thin (1mm) needle to be heated at its distal tip by using a standard electro-surgical diathermy unit. This technique shows promise experimentally and from early clinical work (see section 1.3.4.4.). What is needed is a comparative study between ILP and RF electrocautery in order to determine the advantages and disadvantages of each technique; this should be an experimental in vivo animal study in the first instance, and then a controlled clinical comparison, if appropriate.

ILP is still evolving, and there is a need to continually re-evaluate new parameters and techniques, by further in vivo experimental work. The experimental section of this thesis has shown how new findings have dramatically changed the concepts of the mechanism of action of ILP. These have significant implications for the way ILP is applied in practice, and emphasise the need to re-evaluate and optimise the laser parameters used.

7.2.2. IMAGING

ILP would benefit from improvements in all aspects of imaging involved with the technique. This includes better detection of all hepatic and extra-hepatic tumour, more accurate targeting of tumour with image guidance, monitoring of thermal tissue changes during ILP, and evaluating the extent of necrosis after ILP.

For percutaneous destruction of liver tumour to be more widely accepted, greater sensitivity of tumour imaging modalities is needed, since as many as 40% of patients who are thought to have resectable disease on pre-operative imaging assessment are found to have inoperable cancer at laparotomy (Steele et al, 1991), and up to 35% additional lesions are found using intra-operative ultrasound compared to pre-operative imaging (Clarke et al, 1989). Hence, it is likely that a large number of patients would be treated inappropriately with percutaneous therapy, unless significant improvements are made in tumour detection. All of the main imaging modalities, ultrasound, CT and MRI, continue to improve. Advances in ultrasound technology are giving better images with superior spatial resolution. CT arterial portography (CTAP) is currently the most sensitive pre-operative technique for the detection of liver metastases, and this is likely to improve further with the use of spiral CT (Bluemke and Fishman, 1993). Faster sequences (Saini et al, 1989) and new contrast agents are contributing to making MRI of the liver a more sensitive technique for tumour detection. Superparamagnetic iron oxide particles show uptake in the liver caused by phagocytosis by the reticuloendothelial system. The iron oxide particles increase the T2 relaxation time of the normal liver parenchyma, whereas lesions such as liver metastases, which lack reticuloendothelial cells, have T2 relaxation times that are virtually unchanged (Ferrucci and Stark, 1990). Manganese dipyridoxal
diphosphate (MnDPDP) is a promising paramagnetic MRI contrast agent that is incorporated into normally functioning hepatocytes and produces maximum enhancement approximately 30 minutes after intravenous administration. Initial reports for MnDPDP show useful T1 image enhancement with a potential for improved detection of liver metastases (Hamm et al, 1992). Intra-operative or laparoscopic ultrasound have excellent spatial resolution and a high sensitivity for detecting liver metastases. It is not unreasonable to treat small tumours at laparotomy, or even laparoscopically, with ILP. Performing ILP at laparotomy may be particularly suitable for patients who are having a partial hepatectomy and a single small deposit is found at operation in the other lobe; this small lesion could be destroyed intra-operatively by ILP, while the remaining tumour is resected, as planned. The advantage of using laparoscopic ultrasound combined with either laparoscopic guided ILP or percutaneous ILP, is that a full laparotomy is avoided while the improved tumour detection capability of laparoscopic ultrasound is utilised.

Three dimensional (3D) reconstruction of liver images from CT, CTAP or MRI scans have been shown to improve the pre-operative assessment of the resectability of hepatic metastases, and allow planning of a safer surgical approach (Bennett et al, 1991; Soyer et al, 1991); the relationship of the tumour to vessels is shown, as is the 3D extent of the tumour. With newer equipment and more advanced software, 3D imaging is becoming faster and easier to perform. Three dimensional mapping of the extent and location of liver tumours is also likely to allow better treatment planning prior to ILP; the number of needles/fibres to be used, their site of insertion into a tumour, and the number of treatment cycles to be performed can be better planned.

More accurate localisation of the needle/fibre-tips into the desired location within a liver tumour is crucial, and poor targeting is the main reason why some small tumours (less than 3cm in diameter) are incompletely destroyed. This may be aided by using tiny crystals at the needle-tips that emit ultrasonic signals (Kellet, 1992), and better spatial control may be achieved by using a recently developed 3D ultrasound stereotactic guidance system (Gardner et al, 1992). CT guided needle placement can also be significantly improved by using a specially designed body stereotactic system, based on similar principles to brain stereotactic CT guidance units (Onik et al, 1986a). Interventional MR magnets are also being developed, and the multiplanar images obtained are likely to assist greatly in accurate localisation of the target. This does mean that MR compatible needles would have to be used; new, low magnetic susceptibility needles are available and have been used successfully for MR guided biopsies of the head and neck (Lufkin et al, 1987; Duckwiler et al, 1989).

One of the most important aspects of imaging in ILP is real-time monitoring of tissue damage. Although the clinical experience to date has shown that ILP can be safely and effectively applied with a low morbidity, the overall number of patients treated so far has
been relatively small. ILP will be far more clinically acceptable and potentially safer when the final extent of necrosis can be predicted from the changes taking place during treatment. If this can be accurately done, then the problem of targeting described above will be a lesser one, since it will be immediately apparent if the extent of necrosis can be seen not to encompass the full extent of the tumour, and the needle/fibre-tips then resited into the untreated tumour. The immediate tissue changes taking place, which can be monitored, are a temperature rise and protein denaturation. However, even if these are accurately and reliably depicted, it does not follow that the extent of the changes seen immediately will correspond to the extent of necrosis one day or more later. This has already been demonstrated with dynamic CT, which shows little obvious change immediately after ILP, but clearly defines the treated area 24hrs or more later. Ultrasound does show thermal changes during ILP as increased echogenicity which is mainly due microbubble and tissue char formation. However, the margins of the echogenic change are usually irregular, and the image becomes degraded, making the extent of tissue damage difficult to accurately define. Furthermore, ultrasound is not sensitive to tissue temperature, but only to the microbubbles which occur above a certain temperature. There is a need for an alternative monitoring modality, and MRI may have a useful role to play, since the MR signal depends on the structure and dynamics of water-macromolecular interactions (Bottomley et al, 1984). Laser energy (as heat) causes macromolecules to denature, and this may change the number of water molecules in bound and unbound states; the mobility of tissue water is also altered which results in changed relaxation times (Jolesz et al, 1988). Contrast in MR pulse sequences depends on the temperature because both the longitudinal relaxation time $T_1$ and the mass diffusion coefficient of water are dependent on temperature (Cline et al, 1993). The experimental work on MRI of laser-tissue interaction was reviewed in section 2.3.4.2; a loss of signal intensity is consistently seen around the fibre-tip during ILP in vitro and in vivo, but little work has been done to correlate the extent of this signal loss to the final extent of tissue necrosis. More detailed and careful correlative experimental work is needed, with precise definition of the planes which are imaged and then sectioned for pathological assessment. Different MR sequences should be evaluated and optimised. It is likely that some system of calibrating the signal intensity change to the temperature change will be required. If the degree of signal intensity change required to ensure tissue death after a set time can be quantified, then the margins of the tumour can be imaged during ILP and the treatment continued until these requirements are met. Such a policy would allow limitation of the thermal damage to the tumour and a margin of normal tissue, as desired.

One day or more after ILP to a liver tumour, dynamic CT scanning clearly shows the extent of necrosis as a new area of non-enhancement, and residual viable tumour continues to partially enhance. However, for some tumours it has been shown in chapter 6 that biopsies from the edge may be positive for tumour, even if the dynamic CT does
not show any edge enhancement. A careful imaging-pathologic correlation is needed of patients whose tumours have been treated by ILP and then surgically resected, to try to identify how often there is edge recurrence which is not picked up by imaging or core biopsy (since the latter samples only a very small portion of the total tumour volume); in practice, such a study would be difficult to perform. If a good liver tumour animal model is available, then a preliminary animal study could be undertaken to evaluate CT and MRI in differentiating treated from untreated or recurrent tumour. With MRI, various sequences and contrast media could be investigated, to see if viable tumour can be reliably distinguished from necrotic tumour. Functional imaging modalities may help to identify residual and/or recurrent tumour, although they are limited by relatively poor spatial resolution. Positron emission tomography (PET) using fluorine-18-labelled deoxyglucose (FDG) and oxygen-15-labelled water has been used to determine whether recurrent tumour and fibrotic scar can be distinguished from each other based on increased uptake of the radionuclide agent (FDG) caused by increased metabolic activity in the tumour. Early (phase I) clinical evaluation in rectal cancer appears promising (Ito et al, 1992), and extending this principle to differentiating necrotic and viable tumour in the liver following ILP may be worthwhile. Phosphorus-31 MR spectroscopy has shown substantial changes in the P-31 spectra of liver tumours after chemoembolization and local chemotherapy (Schilling et al, 1992); some changes are highly likely after ILP, although they are not likely to be of value for detecting small volumes of residual or recurrent tumour.

7.2.3. CLINICAL WORK

As new experimental findings of practical importance are reported, these should be applied and evaluated clinically, in order to try to verify any potential benefit in their use. Relevant findings from the experimental section of this thesis include the importance of the cladding material of the fibre-tip, the advantage of using the portable diode laser for ILP, the beneficial effects of the presence of tissue charring, and the possible use of histochemical staining to evaluate tumour viability if it appears morphologically normal on standard H & E staining. The importance of charring has been highly relevant, since it should stop other groups undertaking fruitless attempts to find ways of preventing it. Plastic clad fibres are currently being used for ILP, although the fibre type does not matter if the diode laser is being used. This new laser is being used for ILP, and ways of improving the 1x4 coupler efficiency are being sought, and development of a suitable 1x8 coupler for this laser is also being undertaken. It is hoped in the near future to treat some patients with ILP prior to resecting their liver metastases, and then undertake a detailed histological assessment of human tumour treated by ILP. If the finding of a zone of non-viable, but heat-fixed tumour is also found in this setting, then regular histochemical staining of core biopsies of treated tumour will be performed.
Patients most suitable for local therapies, such as ILP, are also likely to be potential candidates for surgical resection - this should always be remembered and surgery offered to appropriate patients, since local therapies are not yet alternatives for surgical removal in fit patients with small volume, unilobar tumour. There are certain indications where local tumour destruction may currently have an important role to play. First is the small solitary lesion located deep within the right lobe that would otherwise require formal right hepatectomy with extensive loss of parenchyma. Second is bilateral disease in which complete resection would fail to preserve enough functional liver tissue. A combined approach with resection of the hemiliver predominantly involved, and ILP of lesions in the remaining half may achieve the therapeutic goal at lower risk. Thirdly, ILP may provide an option for those patients who are unfit for surgery, and those with recurrence following surgery when repeat hepatectomy cannot be justified. With the present limitations of ILP, in order to have a high probability of destroying tumour and a sufficient margin of normal surrounding liver, only those tumours of diameter 2cm or less should be treated.

With the recent development of more effective chemotherapy regimes for patients with colorectal liver metastases, it would seem sensible to combine ILP with systemic chemotherapy, because of the high likelihood of extrahepatic and micro-metastatic disease in these patients. ILP does not treat extrahepatic tumour, which is often present but undetected on imaging. On the other hand, based on the principle of proportional cell kill, systemic chemotherapy active against occult microscopic disease is unlikely to eradicate bulk hepatic tumour (Ensminger and Knol, 1993). It is therefore logical to combine a tumour debulking procedure with systemic therapy. Surgical resection is the most effective debulking modality, but can be used in very few patients, and has a significant morbidity. ILP has many advantages as a debulking procedure, since it is relatively simple to perform, is minimally invasive, has low morbidity, is easily repeated, and does not interfere with chemotherapy. ILP could be used to debulk macroscopic hepatic metastases and chemotherapy used to destroy residual micro-metastatic and extrahepatic disease. Experimentally, a combination of ILP and 5-fluorouracil has been shown to be more effective than 5-fluorouracil or ILP alone in mouse gastric cancer (Narumi et al, 1990). One could also argue for the potential benefits of a continuous infusion chemotherapy regime during ILP, to take advantage of the increased tumour sensitivity to chemotherapy during heat treatment (Storm et al, 1984). It may also be reasonable to carry out aggressive debulking of tumour over a 1-2 month period at experienced referral centres followed by administration of chemotherapy for residual hepatic and occult extrahepatic cancer by the local referring centre. With further improvements in technique, ILP has the potential of becoming a more widely accepted, effective and safe debulking modality.
There is a need for careful further clinical evaluation of ILP, ideally in the context of a prospective, randomised, controlled clinical trial. Such a trial would require large patient numbers followed up over several years, since the ultimate parameter to be tested is patient survival. To have a no treatment arm in the trial is unlikely to be acceptable to patients, and so ILP would need to be compared with another treatment modality. Many oncologists and surgeons enter patients with colorectal liver metastases into chemotherapy trials, and the newer regimes do appear promising. One option for a trial would be to have a group of patients receiving systemic chemotherapy alone, compared to another group receiving chemotherapy and ILP. Only those patients with tumour confined to the liver (from imaging and/or at laparotomy for the primary cancer) should be included and carefully stratified according to the liver tumour volume. Entry criteria into such a trial would need to be strictly adhered to, and quality of life would be an important parameter to assess, since most, if not all, patients suitable for ILP are asymptomatic at the start of treatment.

At present, any benefit of ILP, in terms of improved patient survival, is unproven, although early analysis of uncontrolled data appears promising. Continued research is needed to improve the technique and to evaluate the potential long-term benefits.
APPENDIX

CHAPTER 4 data: Fibre-tips and laser wavelengths.

In all data presented, the first figure represents the transverse width (T) of the necrotic lesion, and the second figure the longitudinal length (L) in millimetres; for the pig liver data (Table 4.9), the third figure represents the depth (D) of the necrotic lesion.

**FIBRE-TIP DATA:**
(Total energy 1000J, 2W for 500s)

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Tables 4.2 and 4.3

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WAVELENGTH DATA:
(Total energy 1000J).

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Table 4.6
_Argon 488nm/514nm laser:_

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**PRE-CHARRED FIBRE-TIP DATA**
(Total energy 1000J)

Table 4.7
_Size of necrosis:_

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**Size of charring:**

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<td></td>
<td>1 1</td>
<td>5 12</td>
<td>5 10</td>
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<td></td>
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<td>4 6</td>
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**METAL NEEDLE-TIP DATA**

(Total energy 1000J)

Table 4.8

5mm Metal needle-tip:

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<th>Power</th>
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<td>15 15</td>
<td>16 17</td>
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</tr>
<tr>
<td></td>
<td>18 16</td>
<td>20 22</td>
<td>20 18</td>
<td></td>
<td></td>
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<td>20 18</td>
<td>18 17</td>
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Table 4.9

Long metal needles and bare fibre, 805nm

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<td>20 17</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>(13 10 11)*</td>
<td>18 13</td>
<td>12</td>
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<td></td>
<td></td>
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<tr>
<td>Metal needle</td>
<td>21 11</td>
<td>7</td>
<td>25 15</td>
<td>14</td>
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</tr>
<tr>
<td></td>
<td>19 14</td>
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<td>25 8</td>
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<td></td>
<td>(15 7 7)*</td>
<td>35 15</td>
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*indicates necrotic lesion adjacent to large blood vessel
CHAPTER 5.1 data: Histopathological assessment.

Power 2W, exposure time 500s.

<table>
<thead>
<tr>
<th>Plastic clad 0.2mm</th>
<th>Silica clad 0.4mm</th>
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</tr>
<tr>
<td></td>
<td>T</td>
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CHAPTER 5.2 data: CT-pathologic correlation

CT density numbers (HU)

Table 5.1 (24hrs):

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Table 5.2 (2 weeks):

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<td></td>
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Figure 5.9

Size of necrosis on CT versus pathology, in mm:

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<td>8</td>
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CHAPTER 6 data:

Table 6.2.

CT density numbers (Hounsfield units) of patients:

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<td></td>
<td>61</td>
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Serial CEA levels in patients with colorectal liver metastases:
First CEA level for each patient indicates the level just prior to the first treatment, and subsequent levels taken at various times (months) after ILP, as indicated. "**" indicates a further ILP treatment (if next to CEA level, the level was taken just before ILP; number of asterisks indicates the number of ILP treatments). The patient numbers correspond to the patients in Table 6.1.

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211
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metastases: Sonographic guidance for applicator placement. AJR 146: 275-278.
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LIST OF PUBLICATIONS

The following papers and review articles have been published during the period of work for this thesis, or are in press:

   Z Amin, JJ Donald, A Masters, R Kant, AC Steger, SG Bown, WR Lees.

2. "Interstitial laser photocoagulation: Evaluation of a 1320nm Nd:YAG and an 805nm diode laser, the significance of charring, and the value of pre-charring the fibre-tip."
   Lasers in Medical Science 1993; 8(2): 113-120.

3. "CT-pathologic assessment of laser-induced necrosis in rat liver".
   Z Amin, W Thurrell, G Spencer, SA Harries, W Grant, SG Bown, WR Lees.
   Investigative Radiology (in press).

4. "Liver tumour ablation by interstitial laser photocoagulation - Review of experimental and clinical studies."
   Z Amin, SG Bown, WR Lees.

5. "Interstitial laser photocoagulation therapy of liver tumours: Clinical results."
   Z Amin, JJ Donald, A Masters, R Kant, WR Lees, SG Bown.

   Z Amin, JJ Donald, MA Hall-Craggs, M Paley, WR Lees, SG Bown.

7. "Interstitial laser photocoagulation of rat liver: importance of fibre type, laser wavelength, and tissue charring."
8. "Local treatment of colorectal liver metastases: A comparison of interstitial laser photocoagulation (ILP) and percutaneous alcohol injection (PAI)."
   **Z Amin, SG Bown, WR Lees.**
   *Clinical Radiology* (in press).

   **Z Amin, WR Lees, SG Bown.**

10. "Laser treatment of metastases."
    **Z Amin & SG Bown.**
    *Hepatic Metastases: Diagnosis and Management* (in press).

11. "Interstitial tumour photocoagulation".
    **Z Amin, SA Harries, WR Lees, SG Bown**
    *Endoscopic Surgery & Allied Technologies* (in press)

    **Z Amin, SG Bown, WR Lees.**

13. “Ultrasound-guided percutaneous laser ablation of liver tissue in a rabbit model.”
    Letter to the Editor.
    **Z Amin, SG Bown, WR Lees.**
    *European Radiology* (in press).
Hepatic Metastases: Interstitial Laser Photocoagulation with Real-Time US Monitoring and Dynamic CT Evaluation of Treatment

Fifty-five liver metastases in 21 patients were treated with interstitial laser photocoagulation (ILP). Tumors were irradiated with a neodymium yttrium aluminum garnet laser via optical fibers passed through 19-gauge needles inserted under ultrasound (US) guidance. Heating of the tumor was evident at real-time US as an expanding and coalescing echogenic zone around the needle tips. After ILP, dynamic computed tomography (CT) showed laser-induced necrosis as a new area of nonenhancement. Necrosis of tumor volume was more than 50% in 82% (45 of 55) of the tumors, and 100% necrosis was achieved in 38% (21 of 55). Metastases smaller than 4 cm in diameter were treated more effectively and required fewer treatment sessions than did those larger than 4 cm. Complications were minor and included severe pain in four cases, persistent pain for up to 10 days in 11 cases, and asymptomatic subcapsular hematoma (six cases) seen with CT. ILP is safe and effective for liver tumor destruction, and US and CT are useful in different aspects of treatment monitoring.

SECONDARY liver cancer presents a common clinical problem worldwide and has a poor prognosis (1). Colorectal cancer is particularly common, with 27,000 new cases diagnosed each year in the United Kingdom (2) and 157,000 cases in the United States (3); over 50% of these patients will develop liver metastases (4). Patients with secondary hepatic tumors rarely survive for more than 1 year following tumor detection (5), although those with secondary tumors from a colorectal, carcinoid, or islet cell primary tumor have a slightly better prognosis (6-9). Treatment options are limited, and only about 5%-10% of patients are suitable to undergo surgical resection (10), with a resulting 5-year survival of 20%-40%, depending on the type and extent of tumor (11-15).

Alternative, palliative treatments such as radiation therapy, hepatic artery ligation, or embolization may have a high morbidity and show no substantial improvement in survival (16,17). More recently, techniques such as cryotherapy (18,19) and percutaneous intrahepatic injection of absolute alcohol (20) have been used to treat liver metastases. Cryotherapy has the disadvantage of requiring laparotomy, since the probe used is too large to be safely inserted percutaneously; intrahepatic alcohol injection results in an inhomogeneous distribution within the tumor and imprecise areas of necrosis (21,22). There is therefore a need for a simple and more precise technique, with low morbidity, for destroying deep-seated tumors in the liver.

Interstitial laser photocoagulation (ILP) is a recently developed, minimally invasive technique of local tumor destruction within solid organs. ILP with a neodymium yttrium aluminum garnet (Nd:YAG) laser was first described in 1983 (23). Tumors are destroyed by direct heating by using low-power laser light energy delivered via thin optical fibers. Experimental work has shown that a well-defined area of coagulative necrosis is obtained around the fiber tip, with minimal damage to surrounding tissues (24,25). Pilot clinical studies have demonstrated that this technique is practical for the palliation of hepatic tumors (26-29). The success of ILP is dependent on delivering the optical fibers to the target area, real-time monitoring of the effects of the treatment, and subsequent evaluation of the extent of thermal damage. The key to achieving these objectives is in the imaging methods used. The ultrasound (US) findings of ILP in the experimental setting have been described (30,31), but the clinical role of US and computed tomography (CT) during and after ILP has been only briefly described in a small series of patients (26-29).

The purpose of this paper is to describe our clinical experience with ILP for liver tumor ablation in a larger series than previously reported and to perform a critical evaluation of the imaging methods used, namely US and CT.

MATERIALS AND METHODS

Twenty-one patients (eight women and 13 men; median age, 65 years; range, 28-77 years) with liver metastases were treated with ILP. The primary tumors were colorectal (n = 15); and gastric, esophageal, renal, colorectal and breast, small bowel carcinoid, and pancreatic islet cell (n = 1 each). Patient details are summarized in Table 1. Admission criteria were flexible, particularly in the early stages of the study, but patients with evidence of extrahepatic disease were excluded. Preferred criteria were less than five metastases with none measuring more than 4 cm in diameter. Adherence to these criteria was greater in the second stage of the study than during the first. The median size of the metastases was 4.1 cm (range, 0.5-18 cm).

Index terms: Lasers, interstitial therapy, Radiation oncology, Interventional radiology, Liver neoplasms, metastases.

Abbreviations: CEA = carcinoembryonic antigen, 5-HIAA = 5-hydroxyindoleacetic acid, ILP = interstitial laser photocoagulation, Nd: YAG = neodymium yttrium aluminum garnet.

Zahir Amin, MRCP • Jennifer J. Donald, FRCR • Andrew Masters, FRCS • Ravi Kant, MD
Adrian C. Steger, MS, FRCS • Stephen G. Bown, MD, FRCP • William R. Lees, FRCR

Address reprint requests to Z.A.

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Table 1
Results of IL P Treatment of 55 Tumors in 21 Patients

<table>
<thead>
<tr>
<th>Patient/ Sex/Age (y)</th>
<th>Primary Tumor</th>
<th>No. of Metastases (cm)</th>
<th>Diameter of Metastases (cm)</th>
<th>No. of ILP Treatments</th>
<th>Necrosis Grade at End of ILP</th>
<th>Survival Since Start of ILP (mo)</th>
<th>Alive or Dead</th>
<th>Chemotherapy</th>
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</tr>
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<tr>
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than 4-5 cm in diameter. Single large lesions were included if they were thought to be amenable to debulking. Patients with inoperable lesions were unfit for surgery or refused operative resection of their liver metastases. Fourteen patients received some form of chemotherapy either before or after ILP treatment. The study had been approved by the local ethical committee and all patients gave informed consent. Pretreatment CT scans (Somatom DR; Siemens Medical Systems, Erlangen, Germany) of the liver were obtained within a few days of treatment and included non-contrast medium-enhanced, dynamic, and delayed (with a wait after contrast medium injection) images. Dynamic CT scanning was commenced following rapid intravenous administration of a bolus of 100 mL of contrast medium (iohexol, 350 mg/mL) (Nycomed, Birmingham, England), and a further 30 mL of contrast medium was given during rapid scanning through the liver. Scanning time totaled 5-6 minutes. All scans were contiguous, with a section thickness of 8 mm. Serum biochemical (electrolytes, urea, and liver function tests) and hematologic evaluation (hemoglobin, platelets, and prothrombin time) was performed before and after treatment. Serum carcinoembryonic antigen (CEA) level was also measured as a tumor marker in patients with colorectal metastases. Blood samples were obtained before each ILP treatment and at various times (usually 1-2 months) following treatment. Urinary 5-hydroxyindoleacetic acid (5-HIAA) levels were measured just before each treatment in the patient with metastatic carcinoid. Immediately prior to the procedure, patients received diazepam (10-15 mg) and pethidine (50-100 mg) intravenously. Antibiotics (cefuroxime, 1.5 g, and gentamicin, 80 mg) were also administered intravenously, and these were continued for 24 hours after the procedure. US scanning was performed with a 3.5- or 5-MHz transducer (650; Aloka, Tokyo). Six tumors (all smaller than 2 cm, in four patients) seen at CT could not definitely be identified with US and were therefore left untreated. After localization of the tumor with US, 20 mL of 1% lignocaine was infiltrated into the abdominal wall at the intended puncture site and down to the liver capsule. This was followed by US-guided core bi-
opsy of the tumor with a spring-loaded instrument (Biopry; Bard Urological, Covington, Ga) and an 18-gauge Tru-cut needle (Biopry-Cut biopsy needle, Bard Urological); a biopsy specimen of at least one lesion was obtained in each patient. With US guidance, four hollow 19-gauge needles (Cook Europe, Bjaevskov, Denmark) were then inserted, into the tumor, at the site of intended necrosis. The needle tips were positioned about 1-1.5 cm apart in the deepest part of the tumor, since this distance has been found to be the most suitable to ensure necrosis of intervening tissue (25). For small (1-1.5 cm) tumors, only two needles per tumor were required.

A freshly cleaved, sterile 0.2-mm optical fiber from a 1 x 4 star coupler fiber splitter (Canstar, Toronto, Ontario, Canada) was inserted down each needle, and the needle was withdrawn slightly, so that 3-4 mm of bare fiber tip lay within the tumor. A bare fiber tip rather than a diffuser tip was used because it has previously been shown that the latter has no advantage in terms of size of necrosis produced or efficiency of light delivery (32). The tumor was treated with laser light (wavelength, 1.064 nm) from a continuous-wave Nd: YAG laser (Flexilase; Living Technology, Glasgow, Scotland) at a power of 2 W per fiber for 500 seconds (total energy, 4,000 J) if one fiber was used. The maximum power that could be transmitted down each fiber was 2 W; higher powers caused damage to the coupler. An exposure time of 500 seconds was chosen because experimental work with the four-fiber system showed that the maximum necrosis occurred with 1,000 J (2 W x 500 seconds) of energy (25). Ensuing tissue changes were monitored with US during treatment.

The needles and fiber tips were carefully repositioned by withdrawing them approximately 1.5 cm, and the treatment was repeated, up to four times per session, depending on the size of the tumor and the thermal changes seen at US. For tumors less than 4 cm in maximum diameter, this maneuver allowed optimal coverage in most cases. For larger tumors, however, to achieve greater areas of necrosis, the needles had to be withdrawn and replaced in a different part of the tumor. This was often limited by the echogenic distortion of the area already treated. This problem has been partly overcome in recent cases by placing eight needles in the appropriate sites within the tumor prior to starting treatment and then performing ILP via the two sets of four needles, one after the other. Some of the earlier cases were treated before the Canstar fiber splitter was available, and in these cases, one to three laser fibers were used, depending on the tumor size and accessibility, and were activated consecutively rather than concurrently. Treatment of up to three tumors was frequently undertaken at the same session, with two to eight needles per metastasis and a maximum of 12 needles per session.

A dynamic CT scan was obtained either at 24 hours (40 treatment sessions) or 72 hours (15 sessions, if the patient was treated just before the weekend) after ILP, to evaluate the areas of treatment-induced necrosis. Early in the course of this study, some patients (after 15 treatment sessions) underwent CT assessment from 6 weeks to 3 months after ILP. Our interpretation of these scans is likely to represent an underestimation of the extent of initial necrosis because of resorption of the necrotic tissue or tumor overgrowth. Five patients underwent CT without contrast medium, delayed CT, and dynamic CT to confirm that dynamic CT was the most suitable for evaluating laser-induced necrosis. The patient with a pancreatic islet cell primary tumor had hypervascular liver metastases and therefore routinely underwent precontrast, dynamic, and delayed CT scanning after treatment.

Laser-induced necrosis was assessed by comparing the dynamic prep- and post-treatment CT scans; these were found to be more useful than the precontrast and delayed scans for this purpose. Laser-induced necrosis was differentiated from spontaneous tumor necrosis by looking for new areas of nonenhancement (indicating avascularity) on the posttreatment dynamic CT scan. Areas of the lesion that still enhanced were assumed to indicate residual viable tumor. Because of the irregular margins of some lesions as well as respiratory variation between scans, accurate comparative volume measurements of tumors and presumed necrotic zones were not possible. Treatment effect as seen at CT was therefore graded, by two radiologists (Z.A., J.J.D.), as follows: grade 1 necrosis—100% of tumor avascularized; grade 2 necrosis—greater than 50% of tumor avascularized; grade 3 necrosis—less than 50% of tumor avascularized. These percentages were calculated by dividing the estimated volume of tumor necrosis on scans obtained after ILP by the estimated total tumor volume on scans obtained before ILP, with the volumes simply defined as the product of the three largest perpendicular diameters of the lesion at CT.

Biopsies of previously treated areas were undertaken frequently, by using an 18-gauge Tru-cut needle with US guidance, to check histologically for the presence of necrotic tissue or residual or recurrent tumor.

If the posttreatment CT scan showed residual tumor, the patients underwent a second treatment within 1-4 weeks. If no residual tumor was identified, ie, a grade 1 necrosis, then CT was repeated at 2 weeks to look for any evidence of recurrence. For patients with large tumors (nine lesions treated early in the study), the aim was to debulk and control tumor growth rather than to completely ablate. For this reason, some patients underwent further treatments up to 8 months after their initial treatment, when there was tumor regrowth.

In patients who had frequent CT scans obtained at varying intervals after ILP, a careful analysis of the images was performed to determine the optimal time for patients to undergo scanning. Two patients had CT scans obtained at 24 hours, 72 hours, and 1 week after ILP. Another two patients underwent ILP at 1-3-week intervals.
RESULTS

The 21 patients had one to 10 metastatic hepatic lesions (median, three) measuring 1–15 cm (median, 3.0 cm) in maximum diameter (Table 1). Most of the lesions were less than 6 cm; four measured 8, 8, 9, and 15 cm, respectively. We no longer treat patients with such large tumors. Fifty-five tumors were treated. There were 70 patient treatment sessions (one to eight sessions per patient; median, three) and 99 tumor treatments (some tumors were treated several times). The total energy used at each session varied from 5,000 to 34,000 J (median, 12,000 J).

The pretreatment CT scans showed hypovascular metastases in all cases, except in the patient with a pancreatic islet cell primary tumor, who had hypervascular metastases. During treatment, changes similar to those seen experimentally in animal liver were seen at US in all tumors treated (30, 31). After a delay of about 100 seconds, there was a gradually expanding and coalescing hyperechoic zone around each fiber tip, resulting from vaporization of fluid and microbubble formation. This gave an indication of the extent of tumor treated. Complete tumor coverage and hence, potentially complete necrosis, was assumed when the whole tumor was occupied by the echogenic zone (Fig 1). The margin of the echogenic zone, however, was usually irregular and poorly defined, and these changes served only as a rough guide to the extent of necrosis, especially in treatment of larger tumors (greater than 3 cm).

Echogenic linear streaks were frequently seen radiating from the treatment area and were thought to be due to conduction of heat and microbubbles along tissue planes and vessels. After 400 seconds of treatment, a plateau effect was seen, with only slight further expansion of the echogenic zone. Thirty to 60 seconds after completion of treatment, the echogenicity of the area decreased, and it became more inhomogeneous. At subsequent follow-up US, there were no distinctive features differentiating necrotic from viable tumor tissue. This is in contrast to dynamic CT, which allowed good differentiation between treated and untreated areas (Fig 2).

Precontrast and delayed CT scans gave no information additional to that obtained with the dynamic scans in evaluation of ILP-induced necrosis. On the precontrast scans, the attenuation of the treated tumor (which is denatured, necrotic, and coagulated) is similar to that of untreated tumor, and the area of treatment cannot therefore be differentiated. On delayed images, the contrast between residual or necrotic tumor and normal liver is not as good as with dynamic scanning (33), except with hypervascular tumors (one patient in our study).

Grade 1 or 2 necrosis occurred in all tumors smaller than 4 cm, compared with grade 2 or 3 necrosis in all tumors larger than 4 cm, and the smaller tumors also required fewer treatments per tumor (a median of one, versus three for larger tumors) (Table 2).

All tumors treated had some evidence of laser-induced necrosis of at least 10% by volume (Tables 1, 3). Grade 1 necrosis occurred only in tumors measuring less than 3.5 cm and required only a single treatment per tumor (Table 3). Once a grade 2 or 3 necrosis was achieved, progress to grade 1 necrosis was not possible despite further treatments. Overall, 82% (45 of 55) of tumors treated showed a greater than 30% reduction in tumor volume (grade 1 or 2), that is, replacement by necrotic tissue as assessed with CT. Figure 3 shows “before” and “after” CT scans of a tumor demonstrating a grade 1 necrosis after ILP. The sites of the fiber tips are frequently recognized as small areas of vacuolation on CT scans; these are presumably due to small areas of tissue vaporization and/or charring at the fiber tip.

The energy used per tumor varied from 2,000 to 24,000 J (median, 12,000 J). Tumors in which a grade 1, 2, or 3 necrosis was achieved required a median energy of 8,000 J, 11,000 J, or 16,000 J, respectively. For tumors with a grade 1 necrosis, those which had been 2 cm or less in diameter required a lower energy deposition (median, 4,000 J), compared with those larger than 2 cm (median, 10,000 J).

Sequential CT analysis was performed to determine when the size of the treatment-induced necrosis would be maximal, and hence the best time to perform post-ILP CT. Several patients underwent CT at 72 hours after

Table 2

<table>
<thead>
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<th>Tumor Size (cm)</th>
<th>No. of Tumors</th>
<th>No. of Treatments per Tumor*</th>
<th>Necrosis Grade Achieved*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4</td>
<td>35</td>
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<td>1</td>
</tr>
<tr>
<td>&gt;4</td>
<td>20</td>
<td>1–5 (3)</td>
<td>2</td>
</tr>
</tbody>
</table>

* Numbers in parentheses represent median number of treatments.

1 Grade 1 = 100% avascularization of tumor at dynamic CT, grade 2 = more than 50% avascularization of tumor at dynamic CT, grade 3 = 10%–50% avascularization of tumor at dynamic CT.

Figure 2. Patient 3. (a) Dynamic CT scan of the liver shows a 5.5-cm metastasis in the right lobe, with a 1.5-cm area of spontaneous tumor necrosis centrally. (b) Twenty-four hours after ILP, there is a well-defined nonenhancing tumor necrosis area in the medial half of the tumor, indicating treatment-induced necrosis. The two small areas of vacuolation represent the sites of the fiber tips.
ILP. These scans showed a similar lesion size and level of nonenhancement to those of the scans obtained at 24 hours. Scans obtained 1 week or more after treatment of four larger tumors (3–3.5 cm in diameter) demonstrated the appearance of a peripheral enhancing rim around the avascularized area (Fig 4). In one case, this rim increased in size by 2 months, but the patient was not available to undergo biopsy. In another patient, who underwent chemotherapy after ILP, the rim disappeared by 6 weeks after ILP, and in the remaining two patients, biopsies of the rim showed residual tumor in one and liver tissue with inflammatory changes only in the other. For smaller tumors, an enhancing rim was not seen, and scanning at various intervals after ILP did not add information to that obtained with the 24-hour or 72-hour post-ILP scans, although the devascularized area was better defined on scans obtained later than 2 weeks after treatment.

Most of the tumors with a grade 1 necrosis have so far been followed up for a relatively short time, and they have, on the whole, remained fairly well defined avascular lesions, with no definite evidence of recurrent tumor. In three patients in whom grade 1 necrosis occurred in treated lesions, sequential CT scans demonstrated a gradual reduction and disappearance of the lesions (Fig 5). Patients in whom a grade 2 or 3 necrosis had been achieved, however, invariably had tumor progression in a 2- or 3-month interval, although evidence of treatment-induced necrosis was still seen.

Biopsies of treated avascular areas visible on CT scans confirmed the presence of necrosis and absence of viable tumor in several cases (Fig 6). A small core of tissue from an 18-gauge Tru-cut needle, however, cannot be relied on to exclude the presence of tumor in a relatively large-volume lesion, even if multiple samples are taken. Therefore, it has not been our practice to perform multiple, frequent biopsies. In 12 cases, there was documented evidence of necrosis on biopsy specimens obtained from corresponding post-ILP avascular areas seen at CT. Biopsy specimens obtained from grade 1 lesions showed necrosis only, with no evidence of tumor. Biopsies from grade 2 or 3 lesions confirmed necrosis from avascular areas (four biopsies) and residual tumor from the enhancing areas (five biopsies). Samples taken from normal looking liver around a previously treated area showed nonspecific inflammation up to 4 weeks after ILP.

Serial CEA evaluations were performed after each ILP treatment in all patients with colorectal metastases who had an initially raised serum CEA level. In no patient, however, was a convincing decrease in CEA demonstrated to be a direct result of ILP. In two patients, CEA levels did normalize, but both patients had received chemotherapy before and after ILP. The patient with carcinoid showed decreases in urinary 5-HIAA levels, which were related to three of her ILP treatment sessions.

Eleven patients who were followed up for 14 months or longer had evidence of disease progression, either with increased liver tumor (n = 6), lung metastases (n = 4), or local colonic recurrence (n = 1). The patients with increased liver tumor had either new metastases or regrowth of the original tumor if a grade 2 or 3 necrosis had been achieved; there was no evidence of tumor regrowth in the region of a previous grade 1 lesion.

Ten patients had evidence of overall tumor reduction, but their follow-up has so far been less than 1 year (median, 5.5 months). Three of these patients (nos. 1, 8, and 21) had CT evidence that their only metastases (one or two) had been completely avascularized, and there has been no evidence of recurrence at 9, 4, and 6 months, respectively.

Survival data of the patients since ILP are given in Table 1. The patient with the longest survival, more than 3 years, had colorectal metastases; eight (38%) patients survived for at least 1 year, and a further seven (33%) for 6 months or more. Of the 21 patients, 14 are still alive, with a median survival to date of 7.5 months (range, 4–29 months).

ILP treatment was well tolerated by most of the patients, regardless of the number of tumors treated. Mild abdominal discomfort during treatment and for 24–48 hours afterward was common. Additional analgesia was often required for lesions just under the liver capsule, either for shoulder pain due to diaphragmatic irritation or abdominal and/or back pain thought to be due to heat conduction to nearby peritoneum or retroperitoneum. In four cases (two tumors adjacent to the diaphragm and two next to the peritoneum), the pain resulted in shortening of the treatment time.
with intermittent bouts of 100–300 seconds rather than continuous 500 seconds; the treatment was completed, however, in all four cases. A marked bradycardia occurred in one patient during treatment of a lesion in the tip of the left lobe and was thought to be due to stimulation of vagal branches in the adjacent stomach wall. All patients were hemodynamically stable in 24 hours after ILP, but subsequent CT scanning demonstrated small subcapsular hematomas in four cases, and in one case, there was a drop in hemoglobin by 20 g/L after two treatments administered 1 week apart. A rise in serum transaminase levels occurred in most of the patients after ILP, except when there was limited treatment to a small tumor volume. At 24 hours after ILP, this rise varied from 1.5 to 8 times the levels before ILP but always returned to normal by 3–14 days. This would be consistent with a transient inflammatory response in the liver adjacent to the treated areas, especially if two or three metastases were treated in one session. In six cases, small pleural effusions were seen on CT scans obtained after ILP treatment of lesions close to the diaphragm, but there were no respiratory symptoms, and the effusions had resolved by the time of the following treatment session. All patients were discharged by 24 hours after ILP, although on 11 occasions, patients required analgesia administered orally for up to 10 days. A transient and mild elevation of temperature was reported in several cases 24–72 hours after treatment, which was probably due to the presence of necrotic tissue in the liver.

**DISCUSSION**

This study showed evidence of laser-induced tumor necrosis in all 55 liver metastases, with only relatively minor complications. Greater than 50% reduction in tumor volume (grade 1 or 2) was achieved in 82% (45 of 55) of tumors treated and in 68% (13 of 19, two still being treated) of patients. This response compares favorably with that achieved with other palliative, nonsurgical methods of treating liver metastases, which have significant morbidity and no convincing survival benefits (16,17). Regional intraarterial chemotherapy for liver metastases produces a significant response (defined as 50% or greater reduction in tumor volume) in 40%–60% of patients, but when it is given systemically, the response rate is only 17%–21% (34–37). Unlike chemotherapy, all tumors treated with ILP show some response, although if chemotherapy is effective, it has a more global effect on microscopic and extrahepatic disease when given systemically.

Grade 1 tumor necrosis (indicated by 100% avascularity on CT scans) was achieved by performing ILP until the whole tumor was encompassed by an echogenic zone at US and including an approximately 1-cm margin of surrounding normal tissue to destroy any undetected extension of tumor. Grade 1 necrosis implies an assumption that the avascularity (or nonenhancement) on CT scans is indicative of necrosis with nonviable tumor. Although this can only be proved with detailed histologic correlation, it is a logical assumption for three reasons. First, necrosis was confirmed in several biopsy specimens of avascular parts of a lesion after ILP; second, experimental work with normal livers, using the same laser parameters, shows a well-defined area of coagulative necrosis that corresponds to angiographic evidence of loss of all small and some large vessels in the treated area (24,25). Third, the temperatures reached at the fiber tip are over 100°C, and those 8 mm from the tip are over 50°C (24), making it highly unlikely that tumor cells can survive these temperatures for the treatment time of 500 seconds. Takayasu et al correlated CT images of liver tumors treated by means of hepatic arterial embolization with pathologic specimens after surgical resection and found nonenhancing areas to correspond well to treatment-induced necrosis (38).

Healing of the necrotic lesion is by fibrosis and regeneration; for a 3-cm-diameter lesion in normal liver, up to 1 year is required for resorption of necrotic tissue and regeneration of normal liver to be complete (25). This is consistent with our three cases in which grade 1 lesions slowly disappeared after ILP.

US has a useful role in ILP of liver tumors: It can be used to confirm the pretreatment CT findings and may allow detection of further lesions not seen with CT, although lesions seen at CT may sometimes not be visible at US. In experienced hands, US allows accurate needle-tip positioning into the desired sites within the tumor. Real-time imaging of the treated area as a developing and enlarging echogenic zone has been reliable in pre-
Figure 5. Patient 18. (a) Dynamic liver CT scan obtained before ILP shows an inhomogeneous 3-cm metastatic deposit posteriorly. (b) A large area of necrosis and vacuolation is seen after ILP. (c, d) Dynamic CT scans obtained (c) 2 months and (d) 6 months after the final ILP treatment show gradual resorption and reduction of the necrotic area with replacement by regenerating liver.

Figure 6. Patient 17. A biopsy specimen obtained 1 month after ILP shows coagulative necrosis and inflammatory cells, with no viable malignant cells. (Hematoxylin-eosin stain; original magnification, ×40.)

dicting the extent of necrosis in treatment of smaller (less than 3-cm-diameter) metastases (29,39). Difficulties arise in the treatment of larger lesions, due to degradation of the US image by echogenic material and subsequent problems in clearly identifying remaining tumor as well as in seeing the needle tips. This could result in areas of tumor escaping treatment; the presence of echogenic changes, however, provides an indicator that thermal damage is occurring. US is also unhelpful in evaluation of lesions after treatment, since ILP produces well-defined, solid areas of coagulative necrosis with US characteristics fairly similar to those of tumor tissue. This similarity in US appearance between treated and untreated tumor made subsequent targeting of the residual tumor difficult, and was the main reason why it was not possible to progress from a grade 2 or 3 necrosis to a grade 1 necrosis, despite several treatments.

Dynamic CT shows the results of ILP clearly as well-defined, nonenhancing areas, and these areas are easily distinguished from untreated enhancing tumor. The optimal time to perform the post-ILP CT assessment is after 1-4 days, which corresponds well with the time at which an experimentally induced necrotic lesion has its maximum size (24). Maximal lesion-to-liver contrast at CT occurs 2-3 minutes after intravenous administration of contrast medium (33), and most hypovascular nonnecrotic lesions gradually become isoattenuating after this time. Necrotic lesions, however, are likely to take much longer to become isoattenuating (40), which is why our scanning time of 5-6 minutes still gives good lesion-to-liver contrast.

Dynamic CT scans were more useful than precontrast or delayed scans in evaluation of treatment-induced necrosis. Delayed CT scanning was performed prior to ILP because some hypervascular tumors become isoattenuating to normal liver during dynamic contrast-enhanced scanning (41); this was seen in one patient whose liver metastases were secondary from a pancreatic islet cell tumor.

The enhancing rim that sometimes appeared around a grade 1 necrotic lesion between 1 and 4 weeks after ILP (Fig 4) can pose a problem, because CT does not allow differentiation between inflammatory change, regenerating liver, or recurrent tumor. Histologic specimens from this rim exhibited inflammatory change in one case and recurrent tumor in another case. The enhancing rim should be viewed with suspicion of possible tumor recurrence, especially in tumors 3 cm or larger before ILP. In these cases, it would be prudent to repeat CT scanning 3-4 weeks after ILP, and if an enhancing rim is found, guided biopsies of this area should be undertaken. Otherwise, CT 24 or 72 hours after ILP gives adequate information about the extent of necrosis, and this interval is convenient for performance of CT.

US-guided liver biopsies with 18-gauge Tru-cut needles confirm necrosis in selected areas that have been treated with ILP (Fig 6). This is not a reliable way of evaluating complete tumor necrosis, however, because even multiple biopsies will give information on only a limited volume of liver, and accurate sampling from a specific area seen at CT, such as an enhancing rim, is not easy to perform. Since the ILP treatment can easily require up to 12 needle passes, there is a theoretical risk that undertaking additional multiple 18-gauge Tru-cut biopsies may cause significant hemorrhage. CT-guided biopsies may be of use in sampling enhancing margins, but localization of the needle tip within fairly narrow rims of tissue may present problems. The only way of confirming absence of viable tumor is to resect the lesion after treatment, but this is unlikely to be a practical or feasible option in most patients.

Although experimentally, with a four-fiber system, a 4-cm-diameter area of necrosis is consistently obtained in normal liver, 40% of tumors measuring less than 4 cm (14 of 35, Table 2) failed to show 100% avascularity (grade 1 necrosis) at CT after ILP. The most likely explanation for this is problems with tumor accessibility and subsequent difficulty with accurate needle placement. Another reason may be the absorption characteristics of laser light by the tumor compared with those of normal liver.
Tumors are inhomogeneous lesions with a variable blood supply, as opposed to relatively homogeneous normal liver. Absorption of laser light is dependent on the presence of blood in tissue (42) and hence on the vascularity of the tumor, and it may also depend on the type of tumor; in addition, the temperatures reached around the fiber tip depend on the local circulation and cooling by flowing blood. Thus, the laser parameters that give a well-defined and reproducible lesion in normal liver may result in a nonuniform and less predictable lesion in tumors. Because of these factors, it is not practical to have a fixed deposition of laser energy for any given tumor size; ILP to tumors of the same size may result in a variable necrosis, despite use of the same amount of laser energy.

The number of treatments performed per metastasis in this series was variable. This was due to the factors outlined above as well as to limitations of procedure time and the need to treat more than one deposit during the same session in some patients. Often, with more extensive disease in some of our earlier patients, the intention was to substantially debulk tumor rather than completely eradicate it, so time was better spent in treating several lesions rather than in attempts to achieve 100% necrosis of a single lesion. The rationale for this was based on improved survival of patients who have limited disease compared with those who have more extensive liver involvement (7,43). We now select patients with smaller tumors (ie, less than 4 cm), and the intention is to completely ablate the tumor.

Monitoring of the biological marker CEA in patients with colorectal liver metastases did not show any clear ILP treatment-related decrease during follow-up. All of these patients had a Dukes grade C colorectal carcinoma at the time of resection of their primary tumor, and most patients had substantial tumor volume when referred for ILP. Although CT of the abdomen and pelvis and chest radiography showed no obvious extrahepatic disease, it is likely in patients with a Dukes C carcinoma. Also, in only three patients (two with colorectal primary cancer and one with a renal primary cancer) was complete tumor avascularization of all lesions achieved according to CT criteria; one of the patients with a colorectal metastasis never had an increased CEA level, and in the other patient, the CEA level rose after ILP.

Selection of some lesions invariably meant progression of other lesions during the treatment interval. These factors may account for the continued rise in CEA level seen in most patients. Careful monitoring is necessary in patients who have surgically resectable disease and in whom ILP is performed because they are either unfit for or refuse surgery. The patient with carcinoid had a reduced urinary 5-HIAA level related to three of the ILP treatment sessions and associated with an improvement of symptoms. The fact that there was a rise in 5-HIAA levels following four of the treatments may be related to which of the metastatic deposits was treated; only those carcinoid deposits that secrete 5-HIAA directly into the systemic circulation (by means of the hepatic venous system) contribute to the urinary levels (44). Hence, one can postulate that only by treating these deposits will there be a decrease in urinary 5-HIAA.

Survival analysis is limited by the small number of patients and the relatively short follow-up time. Of the 16 patients with colorectal metastases, one patient survived for 3 years and 4 months following ILP, five patients have survived for over 2 years (three patients are still alive and two have died), and a further two patients have survived for over 1 year. These figures correspond to 1-year survival of at least 50% and 2-year survival of at least 37%. The 1-year survival of untreated patients with colorectal liver metastases varies from 2% to 27%, depending on the degree of hepatic involvement (8,9). After surgical resection, the median 1-year survival from eight studies was 80%, and the mean 3-year survival was 55% (17). Longer follow-up of our patients will give more valid data. Many of our patients also received chemotherapy either before or after ILP, which may well have some effect on survival. This makes reliable survival analysis difficult, and the only way to make valid comments on this is from a long-term controlled trial, with patients receiving either ILP or chemotherapy or both.

ILP of liver tumors can be improved in several ways. Better mapping of tumor distribution by using three-dimensional reconstruction of CT or US scans or magnetic resonance (MR) images will help in delineating the exact extent of the tumor before treatment. US and/or CT stereotactic methods can be used to improve the accuracy of needle placement. For metastases larger than 3-4 cm in diameter, placement of eight or more needles prior to ILP will allow much more effective necrosis. Four needles are used initially, and the fibers are then passed down the other four needles, which have already been accurately placed, thus avoiding the difficult task of changing needle sites in an echogenic field (due to treatment). Development of a 1 x 8 or 1 x 12 fiber splitter would allow larger tumors to be treated in a shorter time, but technical problems with this type of system include excessive heating of the coupler and low power outputs at each fiber tip. Tumors that are difficult to locate at US can be treated by using CT-guided needle placement.

Performance of ILP close to a CT scanner may allow evaluation of the extent of necrosis and depiction of any untreated tumor immediately after ILP. The tumor can then be treated again at the same session. With time permitting and session availability, more extensive treatment of several metastases at shorter intervals would give greater tumor reduction and reduce interval regrowth. Selection of patients with limited disease will increase the likelihood of complete tumor ablation and is more likely to have a positive effect on patient survival.

The high likelihood of extrahepatic and microscopic disease in patients with liver metastases suggests that chemotherapy in combination with ILP would be effective. ILP could be used to debulk macroscopic hepatic metastases and chemotherapy could be used to destroy residual, microscopic, and extrahepatic disease. A combination of 5-fluouracil and ILP has been shown to be more effective than 5-fluorouracil or ILP alone in experimentally induced gastric cancer in mice (45). One could also argue for the potential benefits of a continuous infusion chemotherapy regimen during ILP, to take advantage of increased tumor sensitivity to chemotherapy during hyperthermia (46).

Ways of improving the monitoring of ILP of liver tumors need to be investigated, and some work on the MR imaging of laser-tissue interaction has recently been reported (47,48). MR imaging may have a role in allowing differentiation of regenerating liver from recurrent tumor around the margins of a previously treated lesion. In the future, real-time MR imaging with temperature-sensitive sequences may allow better prediction of the subsequent development of necrosis (49,50).

Progress in the development of ILP...
for liver tumor destruction will be made with improvements in the monitoring methods. US has a useful role in targeting the tumors and in allowing real-time changes to be seen. Dynamic CT 1–4 days after treatment shows treated areas as avascular and can be used for further treatment planning. With appropriate patient selection and further development of monitoring modalities, this technique may offer a practical and minimally invasive alternative to major surgery for eradication of small, deep-seated tumors and debulking of larger ones.

Acknowledgments: We thank Giovanni Buonacorsi, BSc, PhD, and Timothy N. Mills, BSc, PhD, for technical help and support and Michael Tighe, DCRR, for performance of CT scanning.

References
40. Walley MM. Determining the right hepatic CT: how many years will it take ‘til we learn? Radiology 1991; 181:17–24.
Book Reviews

Pediatric Cardiovascular Imaging
Edited by Ina Lynn Dyer Tonkin, MD

This textbook was designed to be not a comprehensive tome on pediatric cardiovascular disease but rather a relatively brief source of information on current imaging modalities for residents and fellows in cardiovascular radiology and pediatric cardiology.

The basis of the organization of this text is the clinical presentation coupled with the plain radiographic findings concerning pulmonary vascularity. The first chapter on imaging, which follows an initial chapter reviewing embryology, discusses specific disease entities in groups defined by the presence or absence of cyanosis with increased or decreased pulmonary blood flow or pulmonary venous hypertension. Subsequent chapters on angiocardiography and ultrafast computed tomography (CT) are organized in the same fashion. This type of organization has been used in many other texts and works well. Unfortunately, in the chapter on echocardiography the author chose a different method of grouping the specific entities for discussion. While this method of organization—left-to-right shunt lesions versus obstructive lesions versus cyanotic disease—does work, comparison of echocardiographic findings with the CT and plain radiographic findings in other chapters could have been simplified if the chapters had been organized in the same fashion. The chapter on magnetic resonance (MR) imaging findings is short and does not cover a wide range of entities but does give the reader an understanding of the segmental approach to diagnosis of congenital heart disease with MR imaging. The editor has included chapters on fetal echocardiography, postoperative chest radiography, and interventional procedures in congenital heart disease, which are frequently not covered in other texts on congenital heart disease.

Overall, this is a well-written textbook surveying the imaging techniques used in diagnosing and evaluating congenital heart disease. It is well worth buying for those who are training in cardiovascular radiology and pediatric cardiology.

Reviewed by Steven L. Mitchell, MD

Percutaneous Venous Blood Sampling in Endocrine Diseases
Edited by Renan Ufacker and Reingard Sorensen

This is a concise text dealing with the practical aspects of venous sampling in the diagnosis of endocrine diseases. Although it is aimed primarily at vascular radiologists who perform transvenous sampling, the text may be of value to clinicians.

There are six easily readable chapters that contain a brief clinical introduction to the underlying abnormality, a short explanation of various diagnostic laboratory tests, a description of the relevant venous anatomy, and a description of the technique for successful venous sampling. A seventh chapter deals with clinical and laboratory evaluation of endocrine diseases.

The organization of each of the chapters is similar and very readable. The quality of the printing, paper, illustrations, and tables is excellent. The authors have, as intended, filled a void in the angiography literature by creating a usable compendium on percutaneous venous blood sampling for hormone assays.

There are no similar texts available, to my knowledge, and the information can be gleaned from the literature only after the expenditure of a great deal of time. The cost of $98.00 can be justified on the basis of the relatively small market to which this text will appeal and its inherent quality. This is the sort of book that should be available in every angiography training program and in the library of anyone who performs venous sampling.

Reviewed by William I. Dittman, MD
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

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Abstract. Interstitial laser photocoagulation (ILP) is a new percutaneous technique of thermal destruction (necrosis) of deep-seated tumours, using low power laser energy. Our purpose was to investigate: (i) the effects of different laser wavelengths on the extent of thermal damage produced; and (ii) the role of charring around the fibre tip during ILP. Forty-five normal Wistar rats (250–300 g) had ILP to their liver (exposed at laparotomy) by inserting a 400 µm optical fibre into the liver, and activating the laser at 1, 2 or 3 W. This was performed at three laser wavelengths (1064 nm Nd-YAG, 1320 nm Nd-YAG, 805 nm diode) using a clean plane-cleaved fibre, and at two wavelengths (1064 nm and 1320 nm Nd-YAG) using a fibre with pre-charring at its tip. The 805 nm and 1320 nm laser wavelengths produced significantly greater necrosis than the 1064 nm, using a clean fibre tip (mean diameters at 2 W were 21.7 mm, 18.3 mm, 8 mm respectively). Pre-charring the fibre significantly increased the necrotic lesion size at 1064 nm (mean diameter at 2 W was 14.7 mm). Using more strongly absorbed wavelengths (805 nm and 1320 nm) and pre-charring the fibre tip give greater thermal damage during ILP, contrary to previously held views that the optimal wavelength for ILP was 1064 nm in the absence of charring.

INTRODUCTION

The concept of interstitial laser photocoagulation (ILP) was introduced in 1983 (1) as a new low power laser technique of in situ tumour destruction: thin optical fibres are inserted percutaneously into the tumours which are then destroyed by direct heating. ILP has been applied clinically to treat tumours of the liver, pancreas, breast, prostate, brain and lymph nodes (2–6).

The original concept of ILP was that the laser light is transmitted and scattered through the target tissue and then absorbed to produce heat, with consequent coagulative necrosis; using a wavelength that penetrates deeply into tissue was thought to be the principle mechanism by which a significant volume of thermal damage occurred around the fibre tip (1, 7, 8). Hence, it has been generally accepted that the Neodymium:Yttrium–Aluminium–Garnet (Nd-YAG) laser with a wavelength of 1064 nm is the most suitable laser for ILP, because it has relatively greater tissue penetration than other medical lasers (1, 9–12). Charring of the tissue around the fibre tip is said to be disadvantageous (1, 7, 9, 12) because it reduces light penetration into the surrounding tissue, which would theoretically give rise to a smaller volume of necrosis. This has led to various attempts to avoid charring during ILP, either by direct cooling of the bare fibre tip (13) or by using various ‘diffuser tips’, which reduce the local power density (12, 14–16).

We have noticed that charring consistently occurred in cases where there was significant necrosis after ILP in rat liver, breast tumours and fibroids—in the absence of charring, either no necrosis or only smaller necrotic lesions were seen. Similar observations, in vitro, have recently been reported by Wyman et al (17).
Our findings prompted us to perform this in vivo study to answer the following questions about ILP: (a) What is the significance of charring around the fibre tip? (b) What is the effect of less deeply penetrating laser wavelengths on the extent of necrosis? (c) If charring is advantageous, can pre-charring the fibre tip, just prior to ILP, result in larger necrotic lesions?

METHODS

Technique of ILP

Forty-five Wistar rats (weight 250–300 g) were used. The rats were anaesthetized with a combination of intramuscular Hypnorm (Janssen Pharmaceuticals Ltd, Oxford, UK) and diazepam (0.3 and 0.5 ml kg$^{-1}$, respectively). A laparotomy was performed using a midline incision, and the middle hepatic lobe brought out onto the anterior abdominal wall. An optical fibre was cleaved and its distal 3 mm of buffer coat and/or jacket stripped, leaving the cladding intact around the core of the fibre. Mode scrambling of the light beam was used to ensure a uniform beam profile at the output end of the fibre (to avoid any 'hot-spots' of very high local power density which may induce charring); the input end of the fibre was connected to the appropriate laser (see below). The desired output power was set and checked using a Coherent power meter (Model 201, Coherent UK, Cambridge, UK). Approximately 1 cm of the optical fibre was inserted into the rat liver, as shown in Fig. 1, and the laser activated. The red aiming beam (HeNe, 633 nm, 2 mW) was easily visible through the liver surface, and any reduction in its intensity or the time taken for it to disappear was recorded. Similarly, any liver surface effects seen during ILP were noted. At the end of the pre-set exposure time the fibre was removed, the liver lobe replaced in the abdomen, and the wound closed. The fibre tip was visually inspected and the power rechecked.

The rat was killed 24 h later, the treated liver lobe resected, fixed in formalin, and then sectioned into 1–2 mm slices perpendicular (transverse) to the fibre track. The maximum

![Diagram of rat liver after ILP with central charring](image)
Interstitial Laser Photocoagulation

transverse length of necrosis and charring (if present) were measured (Fig. 2).

Comparison of laser wavelengths

Twenty-seven Wistar rats were used for this experiment. The laser wavelengths investigated were 1064 nm Nd-YAG, 1320 nm Nd-YAG and 805 nm diode. The lasers used were a dual wavelength (1064 nm and 1320 nm) Nd-YAG laser (Multilase 2100 Technomed, France) and a new high-power diode (805 nm) laser (Diomed-25, Diomed, Cambridge, UK). A 400μm core diameter optical fibre was used for all wavelengths; with the Nd-YAG laser this was hard polymer clad, and with the diode laser it was silica clad. The powers used at each wavelength were 1, 2 and 3 W, and the corresponding exposure times were 1000, 500 and 333 s (keeping the energy constant at 1000 J). Three rats were used at each power setting and wavelength, and the mean size of necrosis and charring calculated from the measured values.

Pre-charring of the fibre tip

Eighteen Wistar rats had ILP performed using the two Nd-YAG laser wavelengths (1064 nm and 1320 nm). A 400μm hard polymer clad fibre was fired with the tip dipped into a drop (approximately 0.1 ml) of rat blood at 4–5 W for a few seconds so that the distal 3 mm of the fibre tip was blackened. Any excess debris was gently wiped off the fibre tip before inserting it into the rat liver. The laser power was set at the desired level of 1, 2 or 3 W (delivered energy 1000 J) before commencing ILP. Again three rats were used for each power setting and wavelength. The results obtained at these two wavelengths using pre-charred fibre tips were compared to the corresponding results with a clean fibre tip.

Statistical analysis

The mean transverse lengths of the necrotic lesions were compared using the Student’s t-test for unpaired data. Regression analysis was performed for the scatterplot of necrosis vs charring.

RESULTS

All rats survived the procedure with no obvious complications. During ILP with the 1064 nm Nd-YAG laser, only mild liver surface effects were seen with localized swelling and some diminution of the HeNe aiming beam after 200–500 s. With the 1320 nm Nd-YAG laser, there was blackening, swelling and distortion of the liver surface, with complete loss of the HeNe aiming beam by 15–60 s. The most dramatic surface effects occurred with the 805 nm diode laser, with loss of the HeNe aiming beam by 10–20 s; mini-explosions were heard during ILP at power settings of 2 and 3 W but only on one occasion at 1 W; on two occasions, at a power of 3 W, the liver surface

Fig. 3. Magnified photograph of three fibre tips after ILP (using an initially clean fibre tip), showing the variable appearance of char around the tip. This was seen as blackening around the circumference of the fibre, on the cladding (single arrows), or at the cut edge of the buffer coatjacket (double arrow). The most distal 1–2 mm of the fibre tip was always free of any char or debris.
ruptured with considerable smoke production. During ILP at 1064 nm and with a pre-charred fibre tip, the HeNe aiming beam always disappeared by 100–200 s, and the surface effects were similar to those seen with the 1320 nm Nd-YAG laser and a clean fibre tip.

Following ILP with the 1064 nm Nd-YAG laser, the fibre tip appeared relatively clean, but it was always charred after ILP with the 1320 nm Nd-YAG and 805 nm diode lasers. The degree of blackening and tissue debris on the fibre tip was variable, but the location of the black char was always around the circumference of the fibre, either on the cladding or at the cut edge of the buffer coat/jacket (Fig. 3). The distal 1 mm of the fibre tip was always free of any char.

On resecting the treated liver lobe 24 h after ILP, a well-defined zone of coagulative necrosis was seen (Fig. 4). This was roughly spherical except at powers of 3 W with the 1320 nm Nd-YAG and 805 nm diode lasers, when it was more ellipsoidal with the long axis parallel to the fibre track. Sectioning the liver lobe revealed a fairly uniform pale area of coagulative necrosis with the 1064 nm Nd-YAG laser, but with the 1320 nm Nd-YAG and 805 nm diode lasers a central black charred area was also present (Fig. 5), often with a small central cavity.

The mean transverse lengths of necrosis and charring for the various powers, at each wavelength and after fibre tip pre-charring, are presented in Tables 1 and 2. The lengths of necrosis from the 1064 nm wavelength using a clean fibre tip were significantly smaller than those from the 1320 nm and 805 nm wavelengths ($p < 0.001$) and those from the pre-charred fibre tips ($p < 0.05$); charring was not seen with the 1064 nm wavelength and a clean fibre tip at the powers used in these experiments. No significant difference in necrotic lesion size was present after ILP with the 805 nm laser and the 1320 nm laser. The length of necrosis increased when increasing the power from 1 to 2 W at all three wave-
Table 1. Mean (s.d.) size of necrosis (mm) in rat liver after ILP using 1000 J of energy and laser wavelengths of 1064, 1320 and 805 nm. The effect of pre-charring the fibre tip and using a wavelength of 1064 nm or 1320 nm is shown in the last two rows.

<table>
<thead>
<tr>
<th>Wavelength</th>
<th>Power</th>
<th>1 W</th>
<th>2 W</th>
<th>3 W</th>
</tr>
</thead>
<tbody>
<tr>
<td>1064 nm</td>
<td>2.7 (2.5)</td>
<td>9.0 (1.0)</td>
<td>9.3 (1.5)</td>
<td></td>
</tr>
<tr>
<td>1320 nm</td>
<td>13.0 (1.7)</td>
<td>18.3 (0.6)</td>
<td>21.3 (3.1)</td>
<td></td>
</tr>
<tr>
<td>805 nm</td>
<td>10.3 (2.5)</td>
<td>21.7 (2.5)</td>
<td>21.0 (1.0)</td>
<td></td>
</tr>
<tr>
<td>1064 nm (fibre pre-charred)</td>
<td>15.3 (1.5)</td>
<td>14.7 (2.5)</td>
<td>18.7 (2.1)</td>
<td></td>
</tr>
<tr>
<td>1320 nm (fibre pre-charred)</td>
<td>12.0 (1.7)</td>
<td>20.7 (1.5)</td>
<td>19.3 (1.2)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Mean (s.d.) size of charring (mm) in rat liver after ILP using 1000 J of energy and laser wavelengths of 1064, 1320 and 805 nm. The effect of pre-charring the fibre tip and using a wavelength of 1064 nm or 1320 nm is shown in the last two rows.

<table>
<thead>
<tr>
<th>Wavelength</th>
<th>Power</th>
<th>1 W</th>
<th>2 W</th>
<th>3 W</th>
</tr>
</thead>
<tbody>
<tr>
<td>1064 nm</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>1320 nm</td>
<td>0.8 (0.3)</td>
<td>4.3 (0.6)</td>
<td>4.0 (1.0)</td>
<td></td>
</tr>
<tr>
<td>805 nm</td>
<td>4.3 (3.1)</td>
<td>7.7 (1.5)</td>
<td>4.7 (0.5)</td>
<td></td>
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<tr>
<td>1064 nm (fibre pre-charred)</td>
<td>3.3 (1.2)</td>
<td>3.5 (0.9)</td>
<td>5.3 (2.3)</td>
<td></td>
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<tr>
<td>1320 nm (fibre pre-charred)</td>
<td>1.3 (0.6)</td>
<td>4.7 (0.6)</td>
<td>4.7 (0.6)</td>
<td></td>
</tr>
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</table>

DISCUSSION

Our data clearly shows that larger necrotic lesions after ILP are associated with charring around the fibre tip. The early loss of the HeNe aiming beam (with the 1320 nm and 805 nm wavelengths) was consistently predictive of charring and greater necrosis than if the aiming beam was visible throughout ILP (with the 1064 nm wavelength). It would be reasonable to assume that the loss of the aiming beam is associated with decreased penetration of the 1320 nm Nd-YAG or diode laser wavelengths. Hence, it can be inferred that decreased tissue penetration of the laser light results in a greater volume of thermal damage than increased penetration, contrary to what was previously thought.

The absorption coefficient of the 1320 nm Nd-YAG wavelength is 10 times greater than the 1064 nm wavelength in saline (18), and it has been shown to be highly absorbed in brain tissue (19). The 805 nm diode wavelength is also more heavily absorbed in soft tissue compared to the 1064 nm Nd-YAG wavelength (20). Our study has demonstrated that during ILP the 1320 nm and 805 nm wavelengths cause charring in liver tissue relatively quickly and at low powers, compared with the 1064 nm wavelength. This is likely to be due to the energy being deposited in a much smaller tissue volume around the fibre tip, resulting in higher temperatures (9), and early initiation of charring. Once charring has occurred, a positive feedback begins, with even less light penetration, higher local temperatures and more charring. Pre-charring the fibre tip allows this cycle to be initiated with the 1064 nm wavelength, with a subsequent
dramatic increase in the size of necrosis. Pre-charring at the 1320 nm wavelength makes little difference to the extent of necrosis, since the charring cycle begins spontaneously with a clean fibre tip. With the tips pre-churred, the size of necrosis obtained by the 1064 nm and 1320 nm was essentially the same at a power of 3W, although at 1 and 2 W there was a significant difference between the two; this cannot be simply explained, since at 1 W the 1064 nm laser gave larger lesions, but at 2 W the 1320 nm laser gave larger lesions. This difference may be related to the amount of char present at the pre-charred fibre tip at the onset of ILP (which was variable), and it may be that if we had a larger number of lesions from which to calculate the means (i.e. more than three) there would be no statistical difference at 1 and 2 W also. Thus, at present, our data does not conclusively show that in the presence of charring the size of necrosis is independent of wavelength.

With the onset of charring around the fibre tip, the laser is essentially acting like a point heat source, rather than a distributed heat source (point optical source) in the absence of charring. Tissue heating and consequent necrosis then occurs as a result of thermal conduction, and the extent of thermal damage depends on the temperature gradients achieved as well as the length of time the tissue is exposed to the elevated temperatures (21). We generally achieved larger necrotic lesions at 2 and 3 W than at 1 W, with a constant energy of 1000 J. This is likely to be due to the slower rate of energy deposition at the lower power resulting in early thermal equilibrium, a lower maximum fibre tip temperature, and a smaller volume in which the tissue temperature is high enough for long enough to cause necrosis.

The plateau observed at 2-3 W may represent the maximum size of necrosis attainable at the energy used (1000 J), but it may also be related to the size limitation of the rat liver model, with necrotic lesions greater than 20 mm often partly extended to the edge of the liver lobe. However, the rat liver does have many advantages: it is readily available and in vivo ILP is easy to perform; it allows direct visualization of some of the effects of ILP (such as loss of aiming beam and surface changes); and it allows accurate localization of the optical fibre. Biological variability exists, but it is less likely to cause major bias in the data compared with a larger animal model, e.g. the fibre tip abutting against a large vessel in the rat liver is unlikely to cause a major reduction in lesion size. The elipsoidal rather than spherical appearance of the necrotic lesion at 3 W implies that the overall volume of thermal damage probably did increase at this power compared to 2 W, although this is difficult to quantify. However, in further in vitro experimental work, we have noticed that the length of the necrotic lesion along the axis of the fibre can increase unpredictably at powers of 3 W or more, once charring is initiated—a cavity forms in front of the fibre tip, and the laser beam continues to fire straight ahead and creates a linear forward track (unpublished data). This problem may be overcome by using metal-tipped fibres, as demonstrated recently by Wyman et al (17).

What can we conclude from this study? We have shown that charring is desirable during low power ILP of liver with a bare fibre tip. Advantage can be taken of this by simply pre-charring the fibre tip, or by using more heavily absorbing wavelengths. There is little difference between the two new wavelengths we have investigated with respect to the final size of necrosis; however, a more controlled tissue destruction is achieved with the 1320 nm wavelength in rat liver. In larger liver models and in humans (or by using lower power levels), it may well be that the 805 nm diode laser effects are well controlled and entirely satisfactory. This new high power semiconductor laser has many potential advantages—it is simple to use, does not require water cooling or three-phased electrical power, and is small, compact and portable (22, 23); this makes it more acceptable to clinicians and very suitable for use in different imaging suites (ultrasound, CT, MRI), since ILP is really an image-guided technique (3, 6). Pre-charring the fibre tip is very easy to perform clinically, by firing the fibre into a few mls of the patient's own blood just prior to ILP. In the short term, this is probably the most practical option, since the 1064 nm Nd-YAG laser is widely installed and used, compared with the limited availability of the 1320 nm Nd-YAG laser and the 805 nm diode laser. The future is likely to lie in the wider availability of high power diode lasers, in which case pre-charring of the fibre tip is unlikely to make any difference to the necrotic lesion size, and would then be unnecessary.

One could argue that since larger necrotic lesions are obtained in the presence of charring with the laser acting as a point heat source, lasers are not necessary at all for the intersti-
tial thermal destruction of tumours. However, lasers have the considerable advantage of being able to deliver a precise and predictable energy dose to a target, which can be accessed virtually anywhere in the body by using very thin, flexible optical fibres. The only other modality which has recently been shown to be capable of causing thermal destruction of deep-seated tumours via a percutaneous route is radiofrequency electrocautery (24). Techniques such as this need to be evaluated and compared with ILP in order to ascertain the advantages and disadvantages of each modality. This also applies to other non-thermal minimally invasive techniques which are currently being developed.

ILP is still in the early stages of evolution, with considerable potential for further improvements. Fibre couplers allow simultaneous firing of multiple fibres, and significantly increase the size of the necrotic lesion (25). The optimal laser parameters for ILP need to be redefined, in terms of the power and exposure time needed with the new wavelengths, or after pre-charring the fibre tip with the Nd-YAG 1064 nm laser. Metal-tipped fibres warrant further investigation, and may be particularly useful in tissues other than liver, which do not so readily char during ILP —this observation has been made in breast tumours using the 805 nm laser (unpublished data). In some tissues (e.g. brain), charring may prove to be undesirable, and in such cases multiple-fibre systems may allow sufficiently large lesions to be produced at lower powers, without inducing charring. In addition, diffusing fibres or balloon-tipped fibres may also be used to reduce the local power density. Such diffuser tips for ILP have previously been shown to be inefficient and less effective than bare fibres (26), but new developments may allow much higher powers to be delivered, with subsequent larger necrotic lesions in the absence of charring (12, 14).

CONCLUSION

This study has shown that charring around the fibre tip during ILP of liver tissue gives rise to larger necrotic lesions than if charring is absent. We have demonstrated this by pre-charring the fibre tip prior to ILP, and also by using more strongly absorbing wavelengths (1320 nm and 805 nm) than previously used (1064 nm). These two wavelengths both give a similar extent of thermal damage after ILP in rat liver. These findings have significant implications for the further development of ILP as an acceptable clinical tool for local tumour destruction.

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