Interstitial Laser Hyperthermia For Solid Organ Tumours.

SUBMITTED FOR THE DEGREE OF MASTER OF SURGERY (M.S)

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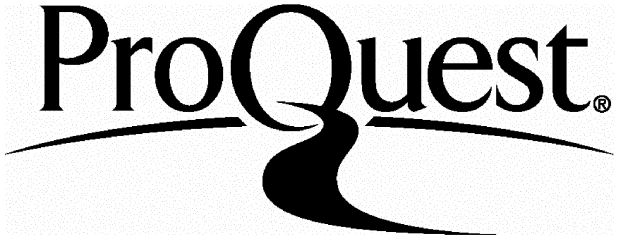

DEDICATION :-

This thesis is dedicated to my wife, Sally and my children James, Harry and Grace.

IMPRESSA :-

We all know what light is, but it is not easy to tell what it is.

Samuel Johnsson 1776

ABSTRACT:-

This thesis describes the potential use of interstitial laser hyperthermia (ILH) to treat certain solid organ tumours. In addition, the influence of tissue optical characteristics on laser tissue interaction is investigated and a novel technique for assessing the extent of laser mediated necrosis is described.

The first 3 chapters give a brief description of lasers in medicine, a review of hyperthermia and discuss the principles and current status of ILH respectively. Chapter 4 identifies areas of research for this thesis with an explanation of the rationale and potential clinical benefits. Chapter 5 discusses the problems of detecting and treating hepatic metastases.

The management of solid organ tumours remains on the whole unsatisfactory. A simple, non-invasive technique is required which can arrest or retard tumour growth. In principle, ILH may fulfil such a role. Chapters 6, 7 and 8 describe the results of clinical feasibility studies treating patients with hepatic, pancreatic and breast cancer using ILH with percutaneous fibre placement under ultrasound guidance. A total of 22 patients were successfully and safely treated. All showed radiological and or histological evidence of at least partial tumour necrosis.

Fundamental to the safe application of ILH in oncology is an understanding of the elements determining the outcome of laser tissue interaction. Tissue optical characteristics is one such factor and chapter 9 studies a subcutaneous tumour comparing reproducibility and the extent of necrosis with normal liver using comparable laser parameters. In liver, the extent of necrosis was significantly larger emphasizing the importance of light scattering in enhancing the biological effect.

Success of ILH depends on matching the extent of laser mediated necrosis to the tissue volume under treatment. Current techniques assessing the extent of laser mediated necrosis in solid organs are relatively crude. Chapter 10 studies a novel approach using laser doppler flowmetery to enhance precision of predicting the extent of necrosis. Results were sufficiently encouraging to merit further work.

Chapter 11 concludes with a brief discussion of future areas of research and development.

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PREFACE :-

The work presented in this thesis evaluates 3 aspects of interstitial laser hyperthermia using the Nd:YAG laser.

The first is a feasibility study using this new technique with percutaneous fibre placement under ultrasound guidance to treat patients with hepatic, pancreatic and breast cancer. This work was carried out in the Department of Surgery, University College and Middlesex Hospitals, London under the supervision of Professors S.G.Bown and M.H.Hobsley.

The remaining work was performed in the National Medical Laser Center within the Department of Surgery at University College Hospital under the direction of Professor Bown. The study on laser tissue interaction in a transplantable tumour was performed to assess the significance of tissue optical characteristic on the extent and nature of the biological effect. Lastily, an attempt is made to improve the precision of predicting the extent of laser mediated necrosis in real time by assessing changes in rodent hepatic microcirculation using laser doppler flowmetery.

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ABBREVIATIONS :-

Alkaline phosphatase	AP
Aspartate transaminase	AST
Carbon dioxide	CO_2
Carcino-embryonic antigen	CEA
Centigrade	^oC
Centimetre(s)	cm(s)
Computerised tomography	CT
Continuous wave	CW
Deoxyribonucleic acid	DNA
Endoscopic retrograde cholangio-pancreatography	ERCP
External beam radiotherapy	EBRT
Fine needle biopsy	FNB
Five Fluorouracil	5FU
Fluoro-deoxyuridine	FUDR
Gamma glutamyl transferase	GGT
Giga hertz	GHz
Gray	GY
Interstitial laser hyperthermia	ILH
Intra-operative radiotherapy	IORT
Intra-operative ultrasound	IOUS
Kilo hertz	KHz
Laser doppler flowmetery	LDF
Liver function tests	LFT
Magnetic resonance imaging	MRI
Mega hertz	MHz
Millimeter(s)	mm(s)
Nanometer(s)	nm(s)
Neodymium : yttrium aluminium garnet	Nd:YAG

Radiofrequency	RF
Ribonucleic acid	RNA
Ultrasound	US
Watts	W
Whole body hyperthermia	WBH

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CHAPTER 1. THE LASER.

1.1 HISTORY OF LASER DEVELOPMENT

LASER is an acronym for **L**ight **A**mplification by the **S**timulated **E**mission of **R**adiation. The fundamental nature of light has occupied the mind of scientists for many centuries. However, It was not until 1867 when James Clark Maxwell came to the conclusion that light was an electromagnetic wave. Further clarification came from Max Plank who in the late 19th century postulated the revolutionary concept of the quantum theory of light. Later, this idea was further developed by Einstein. According to the quantum theory, light is made up of discrete individual packets of energy known as photons.

Fraunhofer (1787-1826) had noticed that for a given element, the wavelength of light absorbed or emitted was restricted to a number of discrete bands peculiar to that element. In 1913, Niel Bohr, applying the newly formulated quantum theory explained this phenomenon on the basis of particles changing between strictly defined energy levels within a given species of atoms. Four years later, Einstein (1917) demonstrated that as well as occurring spontaneously, a particle could return from a high to a lower energy level by interaction with another photon of the correct energy. The newly emitted photon was identical to the incident photon in all respects. This process was termed stimulated emission. If a cascade of repeated interactions with other particles of the same species existing at the higher energy levels could be initiated, then multiple identical photons could be produced leading to amplification of the electromagnetic wave associated with the original photon.

A prerequisite for stimulated emission is that a higher proportion of particles must exist at the higher energy state (population inversion), otherwise the incident photons would be absorbed by the lower energy levels in preference to stimulating the emission of photons from the higher energy levels. Boltzmann's law showed that the distribution of energy population in thermal equilibrium was such that population inversion could not be easily achieved with the vast majority of particles persisting in the lower energy states. In 1953, Townes and his group overcame the problem of population inversion and built the

first 'MASER', the M representing microwaves rather than light. Shortly afterwards Schawlow and Townes (1958) set out the criteria necessary to extend the MASER principle to the infra red and visible light to produce the first optical MASER. The term LASER was coined with the L replacing the M. In 1960, Theodore H Maimen (1960), whilst working at the Hughes Aircraft Research Laboratories constructed the first laser using a small rod of synthetic ruby to produce deep red light at 694 nm.

1.2 PRINCIPLE OF LASER ACTION

The principle of laser action depends upon an input of energy into a lasing medium consisting of a given species of particles existing at more than one strictly defined energy level. The particles must have the capability of undergoing transition from one energy level to another following the emission or absorption of a photon of energy equal to the transition energy between the higher and lower energy level. The transition energy is given by the formula

$$E_1 - E_0 = h\,u \qquad (1.1)$$

where E_1 is the higher energy level of the particle prior to transition, E_0 is the lower energy level after transition, h is Planck's constant and u is the frequency of light which is related to the wavelength by the equation

$$l = \frac{c}{u} \qquad (1.2)$$

where l is the wavelength and c the speed of light. From equations 1.1 and 1.2, the transition energy is given by

$$E_1 - E_0 = h\frac{c}{l} \qquad (1.3)$$

From equation 1.3, it can be seen the transition energy is inversely proportional to the wavelength, therefore the greater the transition between energy levels, the greater the photon energy and hence the shorter the wavelength of light emitted.

When transition occurs, a photon may be absorbed raising a particle from a low to a higher energy state; this is known as stimulated absorption. Alternatively, a particle may

return from a high to a lower energy level with the spontaneous emission of a photon. This process is known as spontaneous emission. A third possibility exists, whereby a photon interacts with a particle in a high energy level with the release of a second photon identical to the incident photon in respect of wavelength, phase, polarisation and direction of propagation. This process is known as stimulated emission (Figure 1.01). If the conditions could be created whereby a photon released by a particle returning to a lower energy level could, by initiating a chain of repeated interactions with other particles existing at the higher energy level then numerous identical photons will be released leading to light amplification. Clearly, this can only occur if the lasing medium contains particles at the higher energy levels; a condition known as population inversion which is bought about by supplying energy to the particles in the lower energy states. This process is known as pumping, which if allowed to take place in a chamber with two aligned mirrors at either end, then the photons travelling along the axis of the mirrors are reflected back and forth producing further identical photons; light amplification will then occur. If one of the mirrors is partially reflective, a proportion of the light will escape. The emitted light will have several unique features.

MONOCHROMACITY - The laser light will only be of one wavelength/colour. Most lasing mediums possess several radiative emission bands which can be made to lase depending upon the transition which may occur. Unwanted wavelengths may be prevented from lasing by a variety of means which allows a desired wavelength to be produced.

COLLIMATION - The emitted laser light is produced in a parallel beam with minimal divergence. This allows the laser beam to be focussed on a very small spot or transmitted by small diameter wave guides. A further consequence of high collimation is that the power density (power per unit cross sectional area in Watts/cm^2) is very high. It is possible to focus the laser beam using a lens onto an even smaller spot to produce even higher power densities.

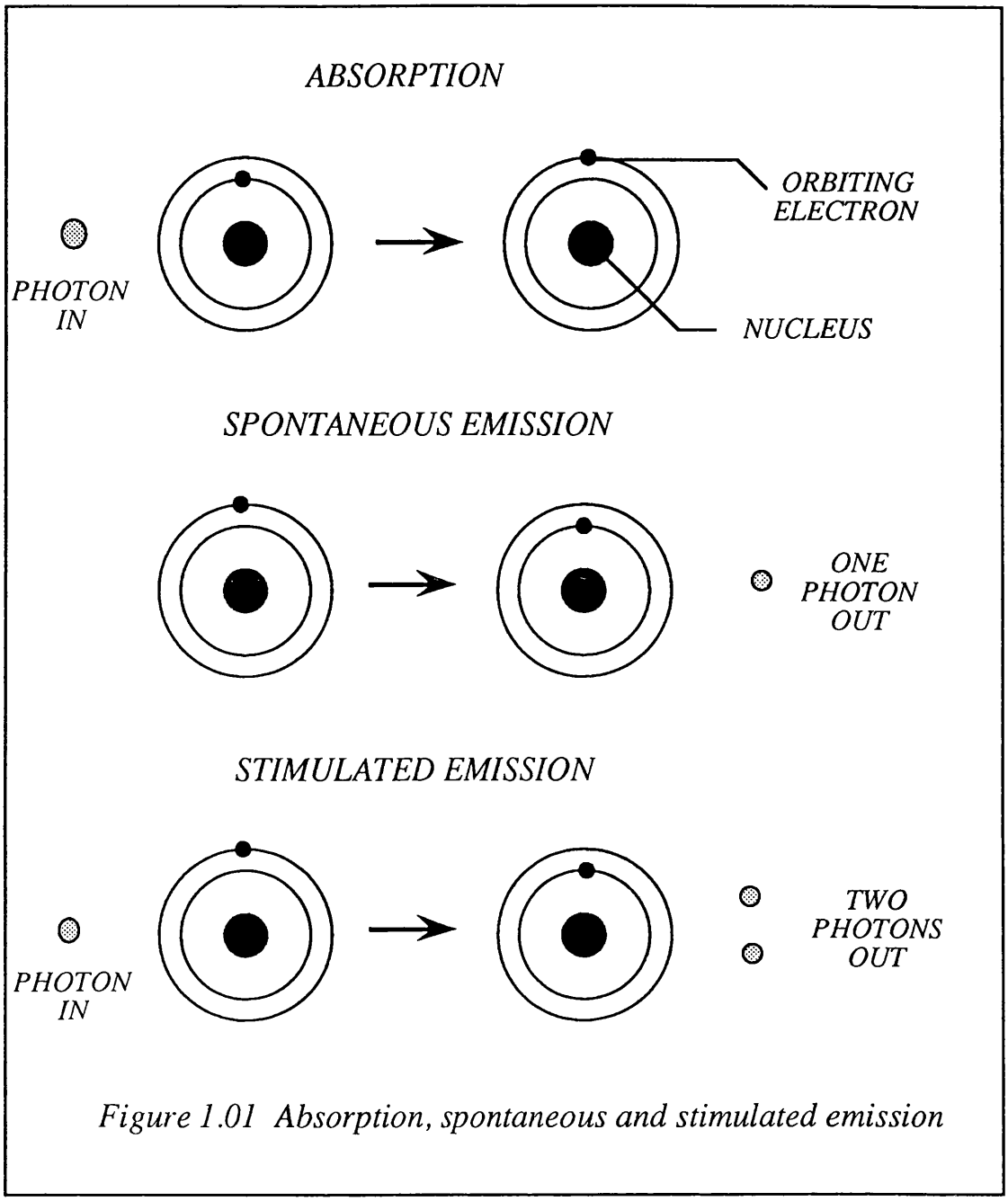


Figure 1.01 Absorption, spontaneous and stimulated emission

COHERENCE - Ordinary light is formed of many wavelengths and is widely divergent. By comparison, laser light exhibits strong temporal and spatial coherence and therefore the waves of laser light are all in the same phase.

All lasers adhere to the basic description given above. A suitable lasing medium is employed which may be solid, liquid or gaseous which is then pumped by an energy source in the form of powerful flash lamps or electrical discharges. The lasing medium is located in a lasing chamber, in addition, apertures, focusing lenses may be employed to modify the output of a laser (figure 1.02).

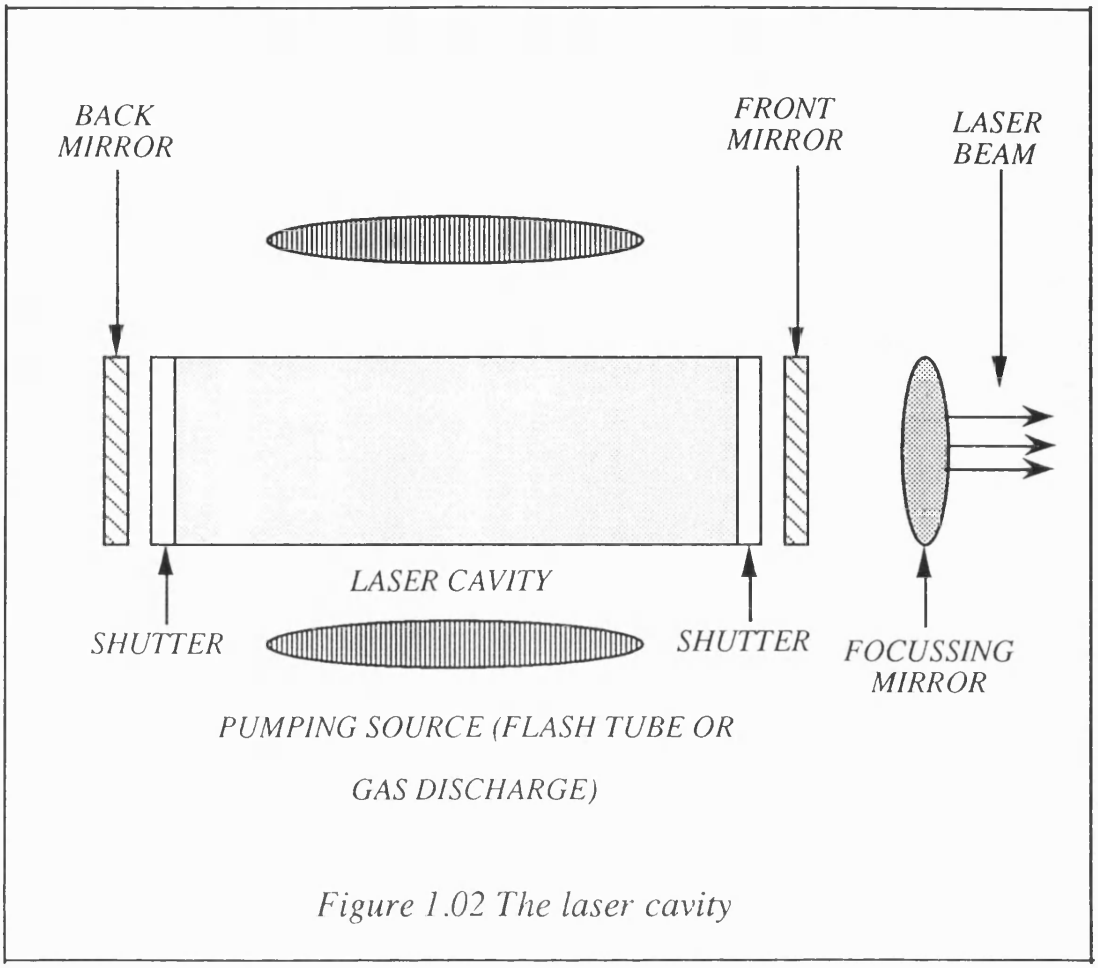


Figure 1.02 The laser cavity

A laser is named after the lasing medium employed to produce a specific wavelength of laser light. The range of lasers used for medical applications varies from CO_2 laser producing laser light in the far infrared at 10 600 nm to excimer lasers where the medium is an excited dimer producing light in the far ultraviolet part of the electromagnetic spectrum.

LASER	WAVELENGTH (nm)
CO_2	10,600
Nd:YAG	1,064
Argon	515
XeCl	308
KrF	249

Table 1.01. Wavelengths of medical lasers

Table 1.01 list the common lasers used in medicine with the respective wavelength of laser light produced.

The radiant energy delivered by a laser can be varied as a function of time in the form of continuous or pulsed waves; this being an inherent feature of the particular laser and a function of the way it is pumped. Each form of laser light delivery can give rise to different types of tissue interaction depending upon the parameters of laser power and tissue interaction time.

CONTINUOUS WAVE OUTPUT

This is defined as a constant power level delivered longer than 0.25 seconds. For example, a Nd:YAG laser can deliver its output for as long as the laser is activated. In most instances, the laser is not targeted continuously, instead, a controlled dose of energy is delivered to the tissue by pre-selecting the duration of exposure either electronically or manually. In addition, a continuous wave laser can be modified to behave like a pulsed laser by rapidly switching the laser on and off or using a shutter (gating/chopping). Typically, gated continuous wave lasers operate with a minimum exposure time of 10 milliseconds.

PULSED WAVE OUTPUT

The pulse duration of a pulsed laser can vary from femtoseconds (10^{-15}) to milliseconds achieving very much higher peak powers than those obtained with a continuous wave laser. Extremely short pulses with extremely high power densities can be created by pulse compression using a process called Q-switching. A Q-switched laser has a shutter placed within the laser cavity. This prevents amplification until pumping has created a high level of population inversion. On opening the shutter, the stored energy is released in a single short pulse (10^{-9} seconds) of very high peak power of typically 10^{9} watts. Mode locking provides a further way of reducing the pulse duration to the order of 10^{-12} seconds.

Various features of common types of medical lasers in use will now be considered.

1.3 TYPES OF LASERS

Of the thousands of wavelengths that have been found to be emitted by numerous lasing mediums, only a few have been of value in clinical practice. The experimental and clinical work described in this thesis was carried out using a Nd:YAG laser. It is therefore appropriate to consider the workings of this laser and by way of contrast, give a brief description of other types of lasers in clinical use.

1.3.1 Nd:YAG LASER

The neodymium in glass laser (Nd:glass) laser was first discovered in 1961 by Snitzer, however, the low thermal conductivity of glass made continuous operation difficult. By 1963, continuous operation of a neodymium laser was achieved. Neodymium doped yttrium aluminium garnet (Nd:YAG) was first operated in the Bell laboratories.

The Nd:YAG is a solid state laser using a synthetic YAG rod doped with a trace quantity of neodymium which serves as the lasing medium. This laser is known as a 4 level laser system (Figure 1.03).

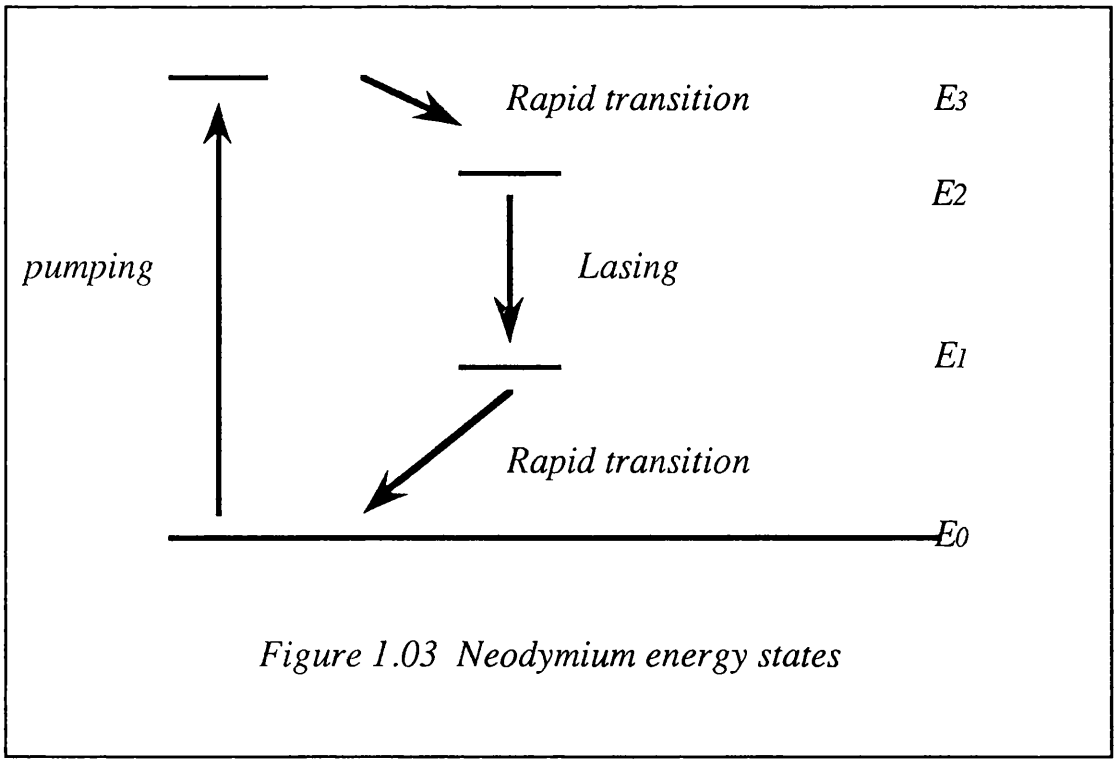


Figure 1.03 Neodymium energy states

A powerful krypton lamp pumps the neodymium atoms into the high energy level (E_3) which then rapidly decay into long lived metastable state (E_2) with the laser action occurring between E_2 and E_3 to produce laser light in the near infra red at a wavelength of 1064 nm. This is quickly followed by rapid decay to the ground state E_0. A coaxial visible red beam of a low power helium-neon laser is used to visualise the Nd:YAG beam. The efficiency of this laser is relatively high at 1-2%, however, a 3 phase electrical circuit and an external supply of cooling water is usually necessary. For clinical use, stable power outputs up to 100 watts are easily achieved which can be transmitted down small diameter fibre optics. In addition to continuous wave operating, The Nd:YAG laser can be Q-switched producing short pulses (10^{-9} seconds) and high power intensities (10^9 watts).

1.3.2 CARBON DIOXIDE LASER

Light in the far infra red part of the spectrum is produced by this laser. The lasing medium consists of carbon dioxide, nitrogen and helium held in an air or water cooled tube. Conventional fibre optics are opaque at the far infra red wavelength which therefore can only be delivered to the tissue by a series of perfectly aligned mirrors located at the joints of rigid articulating arms. Powers up to 35 watts can be generated which is ample for clinical use. The efficiency of the carbon dioxide laser at 15% is relatively high. It therefore can be run using a single phase electrical circuit with no external water.

1.3.3 ARGON LASER

The lasing medium consists of argon gas within a small diameter tube cooled by air or water. As with the Nd:YAG laser, lasing occurs between high energy and a lower energy intermediate state producing a laser light in the blue green portion of the spectrum made up of wavelengths between 437 and 529 nm with four fifths of the output equally divided between 488 and 515 nm. Small calibre fibre optics are capable of transmitting laser light at these wavelengths. The inefficiency of this laser necessitates a three phase electrical circuit with external water cooling.

1.3.4 DYE LASER

The lasing medium may be a dye such as coumarin or rhodamine in a solvent base such as ethanol. Such lasers are able to offer broad spectral tunability because complex dye molecular structures are able offer a large number of excited states of the dye, therefore, emission is not restricted to a single wavelength but spread over a spectrum of about 50 to 70 nm. Different dyes lase within different ranges; selection of the desired emission wavelength is achieved using a birefringent filter.

The efficiency of a complete dye laser system is low predominantly as a result of inefficient ion pump chamber. Peak continuous wave power output of about 1.5 watts are typical of such systems.

1.3.5 METAL VAPOUR LASERS

The vapour state of certain metals can be made to lase, for example, gold producing red light at 628 nm and copper lasing at 511 nm (green) and 578 nm (yellow). In order to produce the metal vapour states, the laser needs to work at very high temperatures.

Metal vapour lasers can only work in a pulsed rather than continuous mode and are able to lase without any mirrors although are rarely used this way. Producing a large number of identical photons per pass of every single incident photon accounts for this phenomenon. The output of a typical copper vapour laser is in the order of 1 millijoule per pulse with a 10 KHz repetition rate producing 10 watts average power.

1.3.6 EXCIMER LASERS

These lasers produce laser light in the ultraviolet portion of the spectrum. The lasing medium consists of a gas whose atoms form diatomic molecules when elevated to the excited state but rapidly dissociate on returning to the ground state. This in turn produces short wavelength high energy ultraviolet light. The term excimer is derived from the words 'EXCited dIMER', although the lasing medium consists of unlike atoms usually a rare gas atom combined with a halogen atom. Table 1.02 lists specific examples of gas/halide excimer lasers with the respective wavelengths of laser light produced.

LASER	WAVELENGTH (nm)
ArF	193
KrF	248
XeCl	308
XeF	351

Table 1.02. Excimer lasers with their respective wavelengths

The output of excimer lasers is pulsed with short pulse duration in the order of a few to a few hundred nanoseconds (10^{-9}).

1.4 LASER TISSUE INTERACTION

Laser light interacts with biological tissue in one of four ways: it can be absorbed, transmitted, reflected, or scattered. Transmitted and reflected laser light produce no biological effect. Absorption can occur directly or following scattering causing laser light to interact with a larger tissue volume. The ensuing biological effect in most instances is relatively less intense and less accurately defined.

The biological response to laser light depends upon light intensity which is a function of the energy density (Joules/cm^2), wavelength, laser tissue interaction time and the optical characteristics of the target organ. The resultant interaction in most cases is thermal with coagulation and/or vaporisation depending on the treatment energy. Applied clinically, such thermal interaction will produce haemostasis of bleeding peptic ulcers and recanalisation of obstructing foregut tumours. The biological effect produced is relatively crude but by turning the power down an order of magnitude, the biological effect of light in the tissue can be more controlled and precise.

In addition, laser light interaction with tissue can yield various non-thermal effects. Non toxic photosensitive compounds taken up preferentially in the stroma of tumours are activated by laser light of the appropriate wavelength releasing photoactive cytotoxic radicles (photochemical reaction). Potential benefit arises from relatively selective tumour destruction without unacceptable damage to surrounding normal tissue. Direct disruption of tissue molecular bonds occur when interaction times in the order of 10^{-9} seconds are used

with high peak pulse powers (photoablative reaction). This is mainly limited to high energy photons, for example, excimer lasers. Ophthalmic surgeons utilise this phenomenon to reshape the cornea for kerato-refractive disorders such as myopia. Even shorter interaction times (10^{-12} seconds) with very high energy densities will strip all the electrons from the atom (electro-mechanical reaction) forming a very localised but very hot plasma - essentially a miniature spark. This causes mechanical disruption of membranes like the posterior capsule which become opaque as a consequence of lens replacement surgery in ophthalmology. Accurate focussing mean power densities are too low to induce damage at non-focused tissue such as the retina. With the development of suitable delivery systems, destructive shockwaves can be generated by Q-switched lasers for fragmenting renal and biliary calculi (photo-acoustic reaction). The point of impact of the laser pulse causes rapid expansion of plasma generating destructive shockwaves.

The factors influencing the biological effect of laser light will now be discussed.

1.4.1 LIGHT INTENSITY

Energy density, expressed as the total energy input per unit area treated (Joules/cm^2) is a measure of light intensity. The thermal effect produced is related to energy density, for example, all other factors being equal, the transition from tissue warming to coagulation and ultimately vaporisation is a function of input energy (Figure 1.04).

An important related concept is spot size - a measure of the surface area upon which the laser light is focused. Spot size is an important determinant of energy density and thus influences the thermal effect produced. Light energy density can be produced by increasing the output but as the density varies as the inverse of the area, then by decreasing the spot size, the energy density can be dramatically increased. Regulating spot size depends on the light wavelength, focusing and the mode of laser light delivery.

1.4.2 WAVELENGTH

Different wavelengths of light have different absorption characteristics. As the wavelength increases through the visible portion of the spectrum into the near infra red,

then light transmission through the tissue deepens with predominant absorption by pigmented tissues. The Nd:YAG laser produces light at a wavelength of 1064 nm (near

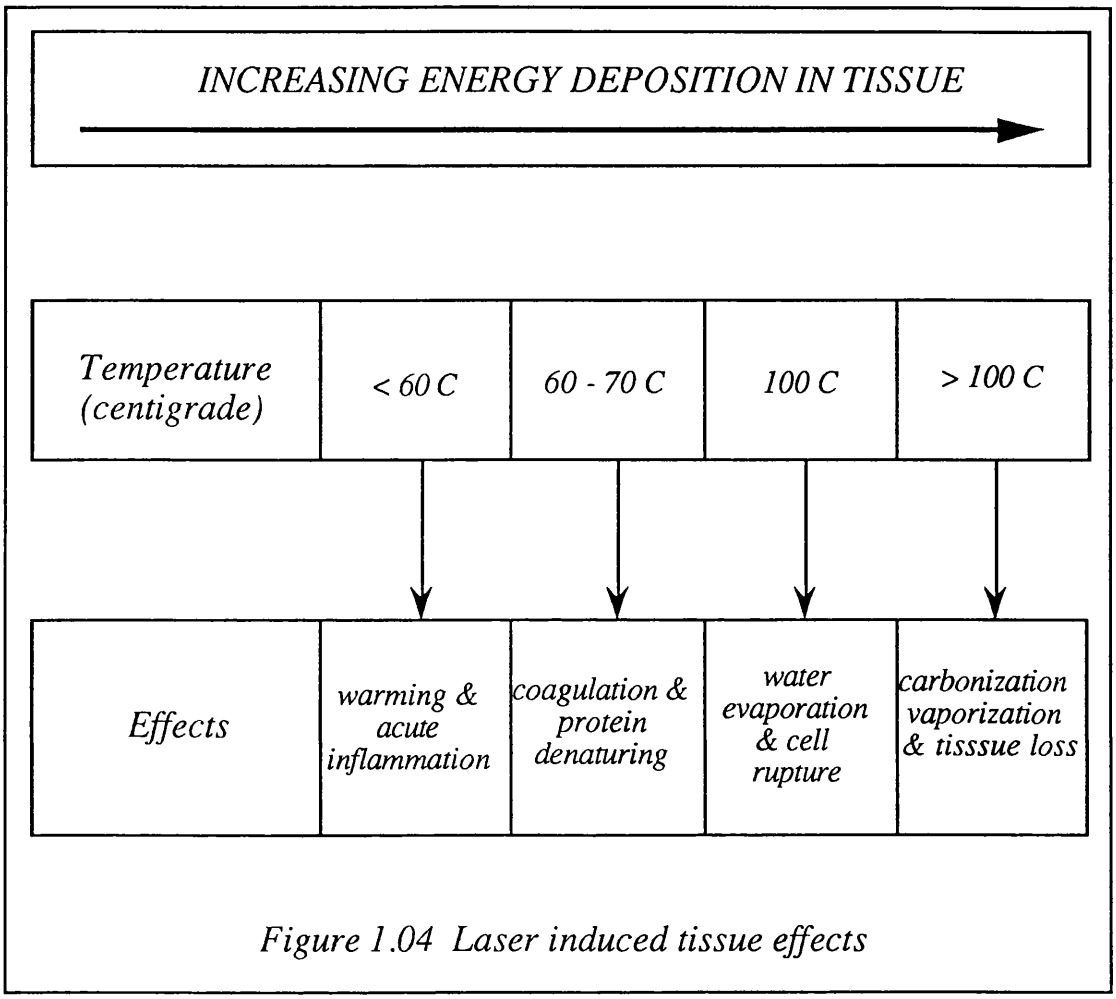


Figure 1.04 Laser induced tissue effects

infra red) which is highly scattered but deeply penetrating compared with the Argon laser producing light at a wavelength of 488 nm (blue) and 514 nm (green). As the wavelength deepens further, for example, the carbon dioxide laser at a wavelength of 10,600 nm (far infra red), then tissue penetration decreases.

The CO_2 laser beam is strongly absorbed by water, thus transmission is strongly attenuated within the superficial tissue layers. These factors give rise to different overall effects at the same power. For example, CO_2 laser light is quickly absorbed by water in the superficial tissues causing well defined vaporisation of small tissue volumes while the Nd:YAG laser with its highly scattered deeply penetrating wavelength produces tissue coagulation in a much larger tissue volume, this effect being comparatively less well

defined. The CO_2 laser is therefore suited to use as a surgical scalpel and the Nd:YAG is much more effective as a haemostatic tool .

1.4.3 LASER TISSUE INTERACTION TIME

Alluded to earlier in this section is how laser tissue interaction varies as a function of different magnitudes of pulse time. Smaller differences in laser exposure times can also have an important bearing on the nature and extent of the desired biological effect. For example, If there is too rapid a delivery of energy required to coagulate tissue, then tissue vaporisation will occur with efficient and rapid dissipation of the input energy. As a result, insufficient time will be available to conduct what heat is available to the surrounding tissue. The net result is an excessive biological effect to a small tissue volume. In contrast, a slow rate of energy delivery to cause vaporisation allows heat to be distributed into the surrounding tissue and any potential benefit will be lost.

1.4.4 OPTICAL TISSUE CHARACTERISTICS

The absorption and scattering of light within biological tissue is a complex phenomenon. The optical characteristics of tissue are represented by two constants, the absorption and scattering coefficients representing the probability of light being absorbed or scattered in a certain distance travelled in a material. In addition, the probability of scattering in any given direction is known as the phase function and is given by the 'anisotropy factor' (g) which is the average cosine of the scattering angle. The three parameters described above cannot be directly measured but can be calculated from other measurements. Biological materials are heterogeneous made up of different layers consisting of various cell types. Figures given are therefore at best an average for a given tissue type.

Calculated parameters are determined from measurements of the transmittance and reflectance of thin layers of tissue at different light wavelengths.There are many models for light distribution in tissue, each one reflected in the results of these calculations. Most workers have calculated absorption and scattering coefficients from the equation derived by Kubella and Munk which was originally described for predicting the effect of the properties

of paint when illuminated by diffuse light. Others use simple Beer-Lambert exponential attenuation with the addition of a correction factor for 'beam broadening' by Yoon et al. Applied diffusion theory or modelling light distribution by the Monte Carlo method have also been used. All methods require assumptions and simplifications to be made making result comparison difficult.

1.5 FIBRE OPTICS

The output of most lasers can be coupled into thin calibre flexible optical fibres of the 'step index' variety which transmit light using the principle of total internal reflection. When a light ray travelling in a medium of high refractive index meets a medium of lower refractive index, the incident light ray is reflected back into the first medium if the angle it strikes the boundary (the angle of incidence) is greater than the critical angle K which is derived from the relationship

$$\sin K = n_2 / n_1 \qquad (1.4)$$

where n_1 and n_2 are the refractive indices of the media.

The step index fibres used in this thesis were made of a central core of fused silica coated by a layer of low refractive index polymer. This is enclosed in a tough plastic sheath for mechanical strength. The very low divergence of a laser beam makes it possible to couple small calibre flexible fibre optics with high efficiency. The major source of loss in laser fibre coupling is at the air/core interface at the input and output ends. This can be minimised by cleaving both fibre ends flat and perpendicular to its longitudinal axis. Typical losses at the input and output ends are 4% with a total transmission for a 1meter fibre of 85-90%.

In clinical practice, most laser applications can made satisfactorily using a single fibre coupled to the laser head. There are however, instances when it is desirable to produce a biological effect in a volume of tissue beyond the maximum attained by a single fibre. This can be overcome using the single fibre but at the expense of repeated fibre manipulations with long and therefore cumulative exposure times. A multiple fibre system can overcome such problems by allowing simultaneous transmission of laser light of near

equal intensity down several fibres using a single laser. Other necessary attributes of a multi fibre system are a rugged compact package with low insertion losses producing stable uniform outputs over sustained laser exposures. Such a system can irradiate large tissue volumes with short exposure times and with more uniform tissue illumination of the treated volume.

There are several ways in which the output of a single laser can be channelled into several output fibres. The simplest way is to use optical components of which there are two main types. The first utilises a series of prisms which split the beam to be fed down the appropriate number of efferent fibres. An alternative technique is to pass the laser beam through a lens made up of several subunit lenses. A different approach for constructing a multi fibre system is to bundle several fibres together using a variety of techniques, one of which is the fused biconic method. The principles of this is to remove the cladding at the point of fusion. The fibres are then heated and placed in precise geometric apposition. The fibre array is then set in an epoxy resin mould to maintain their position. Where the cladding has been removed, a certain amount of transmitted light diffuses into the epoxy resin to be converted into heat. It is possible to quantify such losses and therefore produce couplers to set specifications.

A coupler can be defined as 'a component where any form of beam coupling or splitting involving fibre optic fusion or a conjunction either directly or through some form of integrated waveguide.' Throughout the clinical work described in this thesis, a Canstar 1x4 200 micron coupler (Canstar, Ontario, Canada) was used. This was capable of producing uniform and stable splitting ratios of the laser beam at clinically relevant powers down each daughter fibre (1.5 to 2.0 watts). Losses at the splitting junction were in the order of 30% of the input power.

1.6 DISCUSSION

The clinical part of this thesis aimed to produce laser mediated necrosis in tumours of the liver, pancreas and liver. A potentially suitable laser of this purpose must possesse several features :-

1) The wavelength of laser light must be transmitted effectively down thin calibre fibre optics allowing percutaneous fibre insertion into the target organ.

2) The laser wavelength must be deeply penetrating preferably with some scattering to produce a clinically useful volume of tumour necrosis.

3) The laser must have stable operating characteristics and be suffuciently powerful to run a multifibre system to ensure maximum tumour necrosis.

Although no one laser is ideal, the Nd:YAG laser comes closest to fulfilling the above criteria and was used for all work presented in this thesis.

CHAPTER 2. HYPERTHERMIA.

2.1 HISTORY OF HYPERTHERMIA

The concept of using heat to destroy malignant tissue dates to antiquity. Its therapeutic value was first recognised in ancient Egypt with the earliest reference carbon dated to 1700 B.C. An account is given of breast tumours fulgurated using the glowing tip of a firedrill (Breasted J H., 1930). The ancient Romans and Greeks used heat extensively as a therapeutic tool; its combination of haemostatic and ablative properties were considered particularly valuable (Milne., 1907).

The beneficial effects of heat were also recognized by Hippocrates (370-470 B.C) stating that "those diseases which medicines do not cure, the knife cures; those which the knife cannot cure, cautery cures; and those which cautery cannot cure are reckoned to be wholly incurable". Hippocrates used heat to destroy a growth on the neck of a patient and described in detail many febrile illness and the benefits of the associated fever. In Hindu folklore, the therapeutic benefits of heat were propagated by the Hindu god Susrata who deemed "caustic is better than knife and cautery is better than both."

The impetus to use hyperthermia, that is, induction and maintenance of elevated body temperatures to treat cancer is based on reports of spontaneous tumour remission in patients who suffered episodes of high fever. In a review paper of this topic (Selawry et al., 1957), 150 cases of spontaneous remission associated with the onset of acute febrile illness were encountered out of 450 histologically proven tumours. In the latter half of the 19th century, several reports appeared on the deliberate induction of fever inducing maladies in an attempt to treat malignant disease (Busch., 1866; Fehleisen., 1883). The most prominent came from Coley (1893, 1894, 1911). In a summary of this work, 65 cases of histologically proven but inoperable recurrent sarcomas were treated by interstitial tumour injection of a mixed toxin of Streptococcus Pyogenes and Bacillus Prodigiosus. Ten patients survived 3 to 5 years, 17 survived 5 to 10 years, 7 survived 10 to 15 years and a further 7 survived 15 to 18 years giving a 5 year survival rate of 48% (31/65). All treatments seemed to be well tolerated. Spurred on by Coley's results, several workers used "Coley's toxin" to treat a wide spectrum of malignancies with various degrees of

success. This field was reviewed by Coley's daughter and son (Coley-Nauts et al., 1946). It was noted that at least 15 different toxins of varying potency were used at varying time intervals using different administration routes to a mixture of connective tissue and epithelial tumours considered inoperable at the time of inoculation. Of 312 cases, 192 displayed tumour regression in one form or another with a 77% 5 year survival. Of the 5 year survivors, 15 later died of recurrent disease. The prerequisites for a good therapeutic response were a systemic temperature of 39 to 40^{o}C sustained for several 24 to 48 hour periods. Possible mechanisms of action of Coley's toxins include a direct action of the bacterial toxins on the tumour or induction of an immunological anti-tumour response in addition to any thermally mediated cytotoxic response. Despite the anecdotal nature of this work, its therapeutic implications cannot be denied.

In 1931, a significant step was made in understanding the relationship between temperature and its duration of application to induce cell death. Picus and Fisher (1931) demonstrated with each degree temperature rise in centigrade above 44^{o}C, the time necessary to achieve cell death is halved. Thus for the first time, a rough dosimetric quantification could be made when treating patients.

Warren (1935) treated 32 patients with hopeless widespread metastases arising from a range of primary sites considered beyond the scope of available treatments of the day. Patients were heated in an insulated cabinet initially by diathermy current by direct attachment. The temperature was maintained by radiative heating within the cabinet using high powered lamps. One patient died during treatment but 52% (16/31) showed marked to moderate improvement as judged by extent of tumour shrinkage and speed of emergence of recurrent disease. Median survival from treatment was 8.5 months.

Despite these encouraging results which should have fuelled further research and development in the application of hyperthermia for human cancers, a period of decline followed aided in no small part by the advent of Roentgen's x-rays and the dawn of the era of radiotherapy. However, the failure of radiotherapy as a panacea for all cancers allowed a resurgence of interest in hyperthermia from a scientific and clinical point of view. This commenced in the late 1950's blossoming from the mid 60's onwards.

2.2 *TECHNIQUES FOR INDUCING HYPERTHERMIA*

The definition of "conventional" hyperthermia is based on raising and maintaining tissue temperatures in the range of 42.5-45^{o}C. The ideal technique for inducing hyperthermia should :-

1. Be minimally or non-invasive.
2. Simple to use.
3. Generate reproducible energy outputs which should be easy to control.
4. Produce precise and accurate energy deposition in superficial and deep organs allowing uniform temperatures to be achieved in the heated volume.
5. Utilise reliable equipment which should be efficient, cost effective and of acceptable dimensions.

Despite frequent technical developments, no single system as yet fulfils all these criteria. Heterogeneous tumour histology, tumour volume and anatomical locations make it unrealistic to expect any one system to be satisfactory for all common tumours encountered in clinical practice.

Techniques for inducing hyperthermia are divided in two broad categories - whole body hyperthermia and localized/regional hyperthermia, each enjoying the support of its proponents. The various techniques available and the rationale for their application will now be discussed.

2.2.1 WHOLE BODY HYPERTHERMIA

Coley (1893) injected bacterial toxins into patients with cancer to induce a systemic fever in the hope of producing tumour remission. This constitutes the first description of whole body hyperthermia (WBH) for tumour therapy. The aim of conventional WBH techniques is to raise and maintain core body temperature to 41.5-42^{o}C. The relative thermal sensitivity of organs such as the liver and heart impose a constraint on temperatures that can be safely achieved. Human malignant disease is in most cases a systemic illness. Unlike regional techniques which confine the therapeutic assault on a relatively small

volume of overt disease, WBH is a biologically more attractive treatment concept in attempting to treat overt and occult disease.

All techniques increase core body temperature by reducing patient heat losses combined with an input of thermal energy into the patient. This can be achieved in one of three ways:

1) DIRECT SKIN CONTACT :-

The patient's skin is heated by a surrounding medium, for example, hot wax baths (Pettigrew et al., 1974), heated water blankets (Barlogie et al., 1979) or hot water space suits (Bull et al., 1979). Heat is transferred from the heated medium to the body surface where perfusing skin vessels transfer the heat uniformly throughout the body.

2) EXTERNALLY APPLIED POWER ABSORPTION :-

Non-ionizing electromagnetic radiation delivers heat to the body which is achieved in a variety of ways:

a) Seimans Hyperthermia Blanket (Pomp., 1978) - This consists of a closed system housing a microwave antenna and a radiofrequency induction coil serving as an energy source. The core temperature is raised to 40-42^{o}C within 30 minutes by keeping the air temperature between 53-60^{o}C.

b) Infra red Chamber (Heckel., 1975) - Again this is a closed system irradiated by infra red lamps. The emitted photons penetrate the skin to a depth of 1-2mm producing heat which is distributed throughout the body.

3) EXTRACORPOREAL INDUCED HYPERTHERMIA:-

This technique was first described by Parks et al (1979). Its principle is passing blood from a heat exchanger through a high flow arterio-venous shunt between the femoral artery and vein. Body core temperatures of 41.5-42^{o}C are achieved within 30 to 90 minutes.

Due to thermal sensitivity of organs such as the liver and heart, WBH techniques require rapid and precise control of energy deposition to maintain body core temperatures within safe limits. Extracorporeal techniques possess the greatest potential for rapid and accurate temperature control as they are not dependant on a number of rate limiting heat transfer interfaces which influence response times. A major disadvantage of the

extracorporeal approach is the necessity for cut downs for each treatment to connect the heat exchanger to the shunt.

The technique of WBH, although intrinsically attractive in its attempt to deal with undetected systemic metastases is not without problems (Cronau et al., 1984). An immense stress is placed on the cardiopulmonary system (increased cardiac output by 200%, increased oxygen consumption by 35%). Similarly, renal function is affected (reduced renal blood flow ± a fall in glomerular filteration rate) with associated disturbance in fluid and electrolyte balance. A general anaesthetic is necessary with invasive monitoring to achieve precise control and support of vital functions, fluid replacement and blood gases.

Clearly such demands are undesirable in a patient age group having a high incidence of degenerative disease who may already be compromised by previous chemotherapy and radiotherapy. Reported toxicity include protracted nausea and vomiting, diarrhoea, confusion, pulmonary oedema, myocardial infarction, arrhythmias, hepatitis, disseminated intravascular coagulation, electrolyte abnormalities and peripheral neuropathy (Robbins., 1984). Complex equipment, lack of interest by industry and the unacceptable incidence of complications has resulted in a failure of WBH to be widely accepted.

2.2.2 LOCALIZED/REGIONAL HYPERTHERMIA

The targeting of normal tissue with the risk of vital organ damage is an inherent drawback of WBH. Localized hyperthermia overcomes this by raising the temperature of tumour tissue only. Superficial tumours ($\leq$ 5 cm depth) and deep tumours ($\geq$ 5 cm depth) pose different challenges to physicists and engineers.

For superficial tumours, it is relatively easy to heat tumours with precision but heterogeneity in blood flow often result in non-uniform temperature profiles. The challenge for deeply seated tumours is to provide localized precise heating throughout the tumour volume with minimal normal tissue damage.

There are two basic methods for inducing localized hyperthermia : electromagnetic and ultrasound techniques. Each can be applied using non-invasive or invasive applicators; these are the weakest and therefore the most critical components of the induction system.

2.2.2.1 ELECTROMAGNETIC TECHNIQUES

The term electromagnetic pertains to the oscillation of the energy field between electrical and magnetic field potential with the capacity to enhance one or the other making it the dominant mechanism of tissue heating. Electromagnetic energy can be introduced into the body using one of three techniques : capacitive and inductive modalities (radiofrequency at 0.5-300 MHz) and radiative modalities (microwaves at 300 MHz-30 GHz).

Electromagnetic fields interact with tissue in two ways (Cheung., 1982) 1) Rotation of polar molecules and atoms generating heat due to friction 2) Oscillation of free electrons and ions which collide with immobile atoms and molecules to produce heat.

A) NON-INVASIVE TECHNIQUES

I) CAPACITIVE HEATING

An electrical current which alternates its potential in time (quais-static) is applied between at least 2 electrode plates placed at different points along or near the tissue to be heated. As a result, alternating currents are generated in the tissue perpendicular to the tissue surface and electrode plates generating heat. Tissues of high resistance such as fat induce high power losses within them with subsequent heating of subcutaneous tissues.

The advantages of this technique are the applicators can be modified to individual requirements. Multiple applicators can be arranged in a cross fire arrangement allowing heating fields to be superimposed at a focused point at depth. However, a major disadvantage which is dose limiting is preferential heating of skin and fat. As a result, cooling of applicator surfaces is necessary to facilitate skin protection. In addition, heating patterns are difficult to control and predict while metal temperature monitoring probes can distort the field and give false readings.

II) INDUCTIVE HEATING

This was first demonstrated by d'Arsomal in 1893. Frequencies less than 30MHz are produced by a large coil surrounding the relevant part of the patient creating magnetic fields in the tissue induced by the current flowing in the coil. The magnetic fields oscillate at the radiofrequency thereby generating eddy currents in the tissue leading to heat

generation. An advantage of this method is the induced currents run parallel to the fat and therefore can penetrate without excessive fat heating. However, the induced eddy currents while maximal in the superficial are lowest in the central portion of the treatment volume. As a consequence, there may be minimal heating of the central zone of the treated volume.

Modern inductive equipment is capable of producing cytotoxic temperatures to a depth of 8 to 10 cm with minimal skin and subcutaneous tissue heating. No direct application to the patient is necessary making equipment capable of heating large tissue volumes simple. The main disadvantage is poor energy localization leading to inhomogeneous tumour temperatures and unnecessary heating of non-targeted tissue. This occurs because produced heating fields are neither steerable nor alterable.

III) RADIATIVE HEATING

These techniques have been used widely, generally at 27 MHz frequencies and above. Single or multiple antennae are used to propagate energy into the target tissue. Examples of such devices include waveguides, dipoles and spirals. Using multiple antennae, it is possible to focus and steer the heating pattern.

Radiative techniques suffer from an important limitation on the depth of heating achieved. This depends on the frequency and size of applicator used, the latter must be an appreciable fraction ($\geq 50\%$) of the wavelength to be efficient. As the frequency falls the depth of tissue penetration and wavelength increases. Restricting the size of aperture or antenna at low frequencies limits the depth of tissue penetration. To overcome this, it is necessary to increase the antenna size upon which there must be physical limitation. Localisation of energy deposition is in part a function of applicator geometry, thus a compromise between penetration and localization has to be made. Using high frequencies allows easier energy localisation at the expense of penetration while operating small apertures at low frequencies causes less energy to be propagated. This leads to tissue heating near the antenna i.e surface overheating.

To produce deep localized heating, a phased array applicator needs to be used allowing overlap of respective heating fields. This is achieved using several radiative apertures in specific spatial arrangements focused at a given point at a known depth.

Despite using increasing numbers of apertures in increasingly sophisticated arrangements, inhomogeneous heating with non-uniform temperature profiles continue to dog this approach. The question of possible adverse biological effects from radiative techniques remain unanswered. For now, treatment should be performed in shielded rooms.

B) Invasive Techniques

The principal aim of localized hyperthermia is to elevate the temperature of the whole of the tumour to cytotoxic levels whilst leaving the temperature of the surrounding area unchanged or minimally elevated. For the moment, there is no non-invasive technique which can reliably achieve this in every clinical situation. The main problem is indifferent energy localisation leading to non-uniform temperature profiles. These problems are particularly profound for deep seated tumours. Despite obvious disadvantages, workers have investigated invasive methods in an attempt to provide localisation of a thermal field at depth. Three heating techniques have been employed. Each will be considered briefly.

1) Interstitial Radiofrequency Heating

This technique utilises resistive tissue heating by means of radiofrequency (RF) current driven between pairs of implanted electrodes. Insulated flexible RF electrodes with an exposed conductive section have been used because of their ability to restrict heating to a portion of the implanted length thereby allowing treatment of irregularly shaped tumour volumes (Visser et al., 1989). In addition, there is complete sparing of the skin at the entry site and surrounding normal tissue around the electrode.

The geometry of electrode implantation is important; spacing between electrode pairs should not exceed 15 mm and the electrodes should be absolutely perpendicular to avoid 'hot' and 'cold' spots. Difficulties in management of indwelling metal electrodes in critical organs such as the brain is a major drawback.

2) Interstitial Microwave Heating

Radiative heating is achieved by implantable coaxial microwave antennae, each antenna emits separately unlike the paired electrodes necessary for RF heating. Microwave

antennae are capable of deep heating with good penetration into surrounding tissue. As a result, implant density within the treatment volume is acceptable. However, antennae dimensions are a major determinant of the radiated field. Despite wide availability of different antennae length, there is little flexibility in choosing with precision the antenna length and total insertion depth to coincide with specific tumour dimensions. Suboptimal combination of antennae length and or implant length can lead to tissue overheating at antennae entrance site with unacceptable tumour heating patterns.

3) FERROMAGNETIC HEATING

A magnetic induction field generates heat within an array of ferromagnetic needles implanted into a tumour. Heat is then transferred to the tissue by thermal conduction. A degree of thermal regulation is achieved by using an implanted material having a ferromagnetic to non-ferromagnetic transition point (Curie point) set at the desired tumour temperature. As the curie point is approached, the implants lose their ferromagnetism and with it, their rate of heat production. This feature should in theory lead to homogeneous temperatures by compensating for non-uniform tumour blood flow. The absence of any connections between the implants and the power source makes this technique more suitable for deeply seated tumours.

All the invasive techniques discussed have several significant flaws. Surgical implantation is necessary for deep seated tumours making this approach impractical for multiple and deeply seated tumours. Needle implantation within intra-abdominal tumours can lead to damage to adjacent bowel loops whilst leaving needles *in-situ* for multiple treatments is not always feasible. For example, prolonged tissue contact with nickel-copper alloys can produce systemic toxicity. The implants therefore need to be made of or be covered in a biocompatible material. Another problem is once the implant are placed at operation, any post operative manipulation is impossible.

These important practical limitations has prevented the wide acceptance of invasive heating techniques in clinical practice.

2.2.2.2 ULTRASOUND

Ultrasound (US) may be defined as a form of mechanical energy which is propagated through tissue as a pressure wave. US waves (frequency 1-10 MHz) are generated by applying a high frequency voltage across a piezo-electrical transducer which responds to this high frequency signal by vibrating. This creates a pressure wave which displaces molecules as it passes through the tissue generating heat.

Non-thermal interactions include tissue cavitation (Neppiras., 1980), acoustic streaming and radiation forces (Dunn and Pond., 1978). The relatively low speed of sound in tissue (1.5×10^5 cm/s) at US frequencies allows much shorter acoustical wavelengths (1.5 to 0.15 mm) than those used in the electromagnetic range. This avoids superficial tissue absorption to provide deep penetration which is impeded only by bone or air.

The relatively short wavelength of US waves allows easy focusing for more localized deep tissue heating. By using multiple transducers, it is possible to superimpose more than one beam entering the tissue at different points. This enhances penetration and intensity of energy deposition (Hynynen et al., 1987)

The attenuation of US transmission in air renders this technique unsuitable in the treatment of pulmonary and abdominal tumours within hollow viscera. Similarly, high absorption by bone causes pain which may be treatment limiting. Thus tumours in close proximity of bone need to be treated with caution.

2.3 MECHANISM OF HYPERTHERMIA

There is little doubting the evidence for the cytotoxic effects of hyperthermia, however, as yet, there is no single clear description of the mechanism of how cells are destroyed by hyperthermia. Overgaard (1977) in a review of this topic concluded "....the literature is marked by confusion and disagreement as regards the interpretation of heat dependant influences on tumour destruction." Little has changed since.

It is often stated that malignant cells are more sensitive than their normal counterparts to hyperthermia. Could this provide some clues to the mechanisms of heat induced cell damage? Hypoxia, low pH and low nutrition, 3 factors found within tumours have been shown experimentally to enhance thermal sensitivity (Hahn GM., 1975). This

subject has been reviewed several times (Suit and Shwayder., 1974; Strom et al., 1977) and more recently by Hahn (1982). Following close scrutiny of experimental data, Hahn discovered that despite studies demonstrating increased heat sensitivity of malignant cells, there was enough contradictory data to strongly suggest that increased heat sensitivity was not a general characteristic of all malignant cells. He concluded that the difference in thermal sensitivity between normal and malignant cells was small if indeed present at all.

One possible mechanism for thermally induced cell death is disruption of tumour microvasculture (Song CW., 1984). Large differences exist in the effect of hyperthermia on normal tissue and tumour blood flow. Contrary to popular belief, under normothermic conditions, blood flow in some tumours particularly small tumours is greater than surrounding normal tissues. Indeed, blood flow varies considerably amongst different tumours and even within the same tumour. The critical difference between normal and tumour circulation resides in the limited ability of the latter to increase upon heating. As a consequence, heat dissipation is slower leading to higher tumour temperatures. The morphological features of tumour blood vessels explain this. Capillaries within tumours are made of single layered endothelial cells with no external coat of elastic basement membrane. The vessels are usually sharply bent, extremely dilated with abundant sinusoidal openings which are invariably fully open under normothermic conditions. Thermal damage to these capillaries allows blood to leak from the capillaries with a reduction in perfusion pressure leading to vascular stasis. As a result, tumour pH falls which is associated with increased red cell rigidity causing capillary plugging. White cells adhere to vessel walls especially venules as a result of thermal insult. This is associated with luminal obstruction, endothelial cell swelling, lysis of endothelial and tumour cells with an increase in blood viscosity (Song et al., 1980; Edely H., 1980; Partington et al., 1989). Vasodilatation of vessels adjacent to tumours following heating may exert a 'steal syndrome' enhancing the primary effect of hyperthermia. All these proposed mechanisms converge onto a common pathway, that is tumour vessel occlusion with ensuing hypoxia and fall in intracellular pH (Vaupel and Kallinowski., 1987; Vaupel et al., 1988).

Hyperthermia and ischaemia have a complementary effect with increased necrosis in normal (Morris et al., 1977) and neoplastic tissue (Baker and Wright., 1983). It has also

been shown that cells in the S-phase of the cell cycle which are hypoxic, have low intracellular pH and are nutritionally depleted are particularly susceptible to hyperthermia (Bleehen., 1982; Stewart and Gibbs., 1984). These findings have implications for physiological manipulation of tumour microcirculation and environment to enhance thermal response. For example, using vasoactive compounds (hydrallazine and calcium antagonists), or pH lowering agents (glucose) or even degradable microspheres to impair tumour microcirculation.

Many other mechanisms for thermally induced cell damage have been put forward. There is some evidence implicating protein denaturation as an additional process in cell death although DNA and RNA escape damage. It is known that heat induced changes to cell plasma membrane correlate with membrane morphology, permeability and cell survival. There are studies showing that cells exposed to heat undergo a variety of nuclear and cytoplasmic changes with disturbances in metabolism and macromolecular synthesis (Wheatly et al., 1989; Kampinga et al., 1989a; Glass et al., 1985; Leeper., 1985). More specifically, structural and functional changes in the mitochondria have been correlated with loss of cell function. These changes become more profound with higher temperatures or longer exposure time (Arcancia et al., 1989). In addition, hyperthermia disrupts growth factor or hormone induced cell proliferation by affecting hormone-receptor interactions, intracellular signal transduction (Calderwood et al., 1985; Magun and Fennie, 1981). Hyperthermia also induces synthesis of a number of special proteins thought to be involved in protein transport (Chirico et al, 1988) or import into organelles such as the mitochondria (Deshaies et al, 1988). These proteins have been implicated in some instances of thermotolerance. This phenomenon exhibits itself by reduced thermal sensitivity to subsequent thermal insult following initial exposure. Clearly this has important clinical implications for fractionation thermal protocols.

The mechanism of thermally induced cell death is complex and is likely to be multifactorial. Which of the above factors are a secondary phenomena to a dominant process producing cell death is as yet unclear.

2.4 *HYPERTHERMIA AND RADIOTHERAPY*

The therapeutic implication of thermo-radiotherapy is an important one. If it can be shown that therapeutic benefit of X-radiation combined with heat is potentiated without increased normal cell toxicity or heat allows a reduction in the dose of X-ray to a level associated with a reduced incidence of treatment limiting side effects, then thermo-radiotherapy represents a useful step forward. There is good in-vitro evidence that heat sensitizes normal and malignant cells to X-rays (Dewey., 1984; Overgaard., 1985; Leeper., 1985). Such sensitization has been found important in mouse tumour systems (Streffer & Van Beuningen., 1987) while in rodent tumours, the combination of heat and irradiation damages endothelial cells and vascular network (Song et al., 1987; Zyweitz & Lierse., 1988).

Whether such factors are important in human tumours is open to question. A possible synergism between heat and irradiation is likely to be due to some degree of spatial complimentation. It is known that hypoxic cells are highly radio-resistant. While normally oxygenated tumour cells in well perfused areas which are relatively more difficult to heat effectively should be more easily sterilised by radiotherapy. Interestingly, thermal enhancement of X-ray effects occurs at temperatures well below cytotoxic levels (Streffer & Van Beuningen., 1987). In addition, it takes 30% less radiation to achieve the same cell kill when heat is applied (Westra & Dewey., 1971)

Improved clinical response has been demonstrated in several studies where heat and radiation have been used in combination (Kim et al., 1978 & 1982) although comparisons cannot be made due to non-uniformity in treatment protocols. The most conclusive and only randomized trial was performed in dogs (Dewhirst et al. 1984). Efficacy of combination therapy depended on the lowest temperature achieved within the tumour emphasizing the importance of homogeneous tissue heating,

The mechanism of potentiation of X-ray lethality by heat is incompletely understood. The terms X-ray induced sublethal damage and potentially lethal damage denote damage not leading to cell death and changes in survival induced by modifications in the cells environment respectively. Recovery from both these phenomena is reduced or abolished by heat probably by damage to repair enzymes. Another plausible explanation is

that heat converts X-ray induced repairable defects into irreparable ones while repair enzymes remain intact. Support for these hypotheses has come from Sapareto and his colleagues (1979) who demonstrated that heating during rather than before or after irradiation maximizes cell killing.

2.5 HYPERTHERMIA AND CHEMOTHERAPY

This has potentially important clinical applications. If the efficacy of a drug in combination with heat can be enhanced without an associated increase in normal tissue toxicity or alternatively hyperthermia allows a reduction in drug dosage to an extent which reduces the incidence of treatment limiting side effects, then the concept of thermo-chemotherapy is an inherently attractive one. In-vitro and in-vivo work has shown that heat enhances the effects of chemotherapeutic agents (Cohen and Robins., 1987; Hahn., 1979; Engelhardt., 1987; Herman et al., 1989). Of note, several workers have demonstrated in-vitro the effect of several drugs combined with heat on some human tumours is more pronounced than on normal human bone marrow precursor cells (Neumann et al., 1984), traditionally regarded as acutely sensitive to chemotherapy. Synergism occurs because chemotherapy is effective in well perfused tissues where drug delivery is efficient while heat is more effective in poorly vascularized areas.

Hahn (1982) described 3 types of drug-heat interaction based on experiments in animal tumours.

1) Drugs whose action is enhanced linearly with increasing temperature.

2) Drugs whose action is enhanced above a threshold temperature of 43^{o}C.

3) Drugs active only at elevated temperatures.

Drugs showing the strongest favourable reaction with heat include the alkylating agents, nitrosoureas, cisplatin and carboplatin with enhancement occurring at relatively low temperatures in the range 30-42^{o}C. This has important implications due to the practical difficulties encountered in heating human tumours uniformly. The mechanism responsible for such interactions include increased drug uptake (Hahn and Strande., 1976; Meyn et al., 1980), increased DNA damage due to increased chemical reactivity (Meyn et al., 1979 & 1980; Herman et al., 1988) and inhibition of DNA repair (Meyn et al., 1980). It is

important to note that not all chemotherapeutic agents are more active at elevated temperatures (Kampinga et al., 1989b). In conclusion, hyperthermia is unable to overcome drug resistance completely but can increase cytotoxic mediated cell death considerably.

2.6 CLINICAL APPLICATIONS OF HYPERTHERMIA

The vast majority of clinical studies have been non-randomized, uncontrolled with poorly defined treatment protocols used to treat heterogeneous tumour groups. Critical analysis of findings in such studies is difficult since, in most instances, combination treatment modalities have been employed with no control for the effects of each modality alone. This makes makes it impossible to evaluate the relative contribution of each.

In this section, I have attempted to highlight tumours by histology or anatomical site which, on the basis of early studies, have show a worthwhile response to hyperthermia alone or in combination with either radiotherapy or chemotherapy.

2.6.1 WHOLE BODY HYPERTHERMIA

In a non-randomized uncontrolled study, Larkin (1979) and Parks et al (1979) treated 92 patients and 60 patients respectively with advanced malignant disease of various histological types. In most instances, WBH was combined with radiotherapy and or chemotherapy. Larkin reported an overall objective response rate of 43% with complete tumour regression in 4 patients. However, there were 6 procedure related deaths and an unspecified number of patients developed fatigue, diarrhoea and anorexia. Thirty six patients were available for evaluation 1 to 2 months from treatment in Park's series. Of these, 25 (69%) showed radiological and or histological evidence of a response to treatment. It is not clear what influence such responses had on patient survival.

In a similar study, Pettigrew and colleagues (1974) treated 51 patients with miscellaneous but advanced malignancy using WBH alone. He noted very few complete remissions and no cures. There were 5 deaths , 4 occurring within 48 hours from treatment from disseminated intravascular coagulation attributable to extensive tumour necrosis. Retreatment of patients who relapsed proved less effective than initial treatment. Bull et al (1979) achieved an overall response rate of 20% in 14 patients treated with WBH alone or

in combination with chemotherapy. Eleven patients developed mild nausea and diarrhoea while 4 suffered from a peripheral neuropathy.

Despite non-uniformity of treatment protocols, for some common human tumours, WBH with or without chemotherapy and or radiotherapy can achieve an objective response rate of between 10 to 69% depending on response criteria used. In a few cases (< 5%) complete regression may be obtained but the duration of response is disappointedly short (few months). WBH is associated with an appreciable morbidity although improved monitoring and support of patient's vital functions may reduce this. However, the unacceptable incidence of serious complications such as myocardial infarction, pulmonary oedema, hepatitis, disseminated intravascular coagulation combined with complex equipment, long treatment times may explain the failure of WBH to gain wide acceptance.

2.6.2 SUPERFICIAL EXTERNAL HYPERTHERMIA

Growth control of superficially located malignancies (≤ 5 cm from the surface) can produce worthwhile palliation and in some instances an improvement in patient survival. Superficial tumour location allows relatively easy treatment, temperature monitoring and response assessment. In the last 10 years, most work has been carried out using heat combined with chemotherapy and or radiotherapy. Several anatomical sites and histological types have been identified where worthwhile results has been achieved.

I) BREAST CANCER

It has been shown that hyperthermia in conjunction with low dose radiotherapy (< 30 Gray) produces a twofold increase in complete response rate compared to hyperthermia alone (Overgaard, 1989). Several pre-treatment and treatment factors have been identified influencing the outcome of hyperthermia and radiotherapy (Valdagni et al., 1988a; Van der Zee et al., 1986; Kapp et al., 1989). Amongst the most important were tumour size, morphology, radiotherapy dose and a minimal intratumoral temperature.

For locally advanced primary breast cancer in the intact breast, a randomized study has shown improved 2 year recurrence free survival for patients with with stage II and III disease treated with hyperthermia and radiotherapy compared to hyperthermia alone

(Overgaard., 1989). In another study, Hofman and his colleagues (1989) obtained 3 year local control rates of 90% and 27% respectively for T2-3 and T4 cancers respectively. Whilst encouraging, what influence this has on patient survival is unclear.

II) NECK

The palliation of metastatic disease to the cervical chain of nodes and in the surrounding subcutaneous tissue from head and neck primary cancers remains unsatisfactory especially at previously irradiated sites.

Combining hyperthermia with low dose radiotherapy (20-40 Gray) will produce significantly higher complete response rates although larger tumours showed a reduced complete response rate (Valdagni et al., 1988a; Overgaard., 1989). In addition, patients treated with full dose radiotherapy plus heat therapy achieved a higher local control rate compared with those receiving radiotherapy alone (Overgaard., 1989; Arcangeli et al., 1985). In one randomized trial, full dose X-ray therapy (60-70 Gray) combined with hyperthermia achieved a complete response rate at 3 months of 82% compared with a figure of 37% for radiotherapy alone (Valdagni et al, 1988b). No increase in toxicity was noted, although larger tumours achieved lower complete response rates (Valdagni et al, 1989)

III) MELANOMA

Kim et al (1978) attempted to compare the response of malignant melanoma in 24 patients treated using radiotherapy alone and radiotherapy plus hyperthermia using a RF inductive technique. Radiotherapy alone achieved a complete regression rate of 26% while combination therapy produced a 78% complete regression rate with no increase in skin reaction. Numerous other clinical trials have since demonstrated improved complete response rates for cutaneous, subcutaneous and peripheral lymph node metastases from melanoma treated by radiotherapy and hyperthermia compared to radiotherapy alone (Kim et al., 1982 & 1984). Therapeutic outcome was influenced by radiation dose per fraction, tumour volume and sequencing of radiotherapy and hyperthermia. It appears that a proportion of patients obtaining a complete response remained in local control for the duration of their survival.

IV) OTHER SITES

Despite small numbers of patients involved, it has been noted that radiotherapy plus hyperthermia achieves good local control for several histological types of superficial metastases. These include adenoid cystic carcinoma of the salivary gland, perineal recurrence from rectal carcinomas, peripheral lymph node or soft tissue recurrence from Hodgkins and non-Hodgkins lymphoma (Kapp., 1987).

Using individual patients with matched nodules of superficial tumours serving as controls, Marmor and Hahn (1980) demonstrated an objective improvement in treatment response when radiotherapy was combined with hyperthermia (47%) compared to radiotherapy alone (7%).

V) DEEP TUMOURS

Radiative electromagnetic and capacitive radiofrequency (RF) techniques have been employed in the treatment of deep abdominal and pelvic tumours. In most instances, the tumours were recurrent or failed to respond to conservative treatment. Treatment usually comprised of hyperthermia combined with radiotherapy (RT) and or chemotherapy (CT).

GROUP	*TREATMENT*	*PATIENT NUMBERS*	*COMPLETE RESPONSE*	*PARTIAL RESPONSE*	*NO RESPONSE*
Storm et al (1982)	*RF+CT+RT*	*10*	*1*	*2*	*5*
Baker et al (1982)	*RF + CT*	*59*	*1*	*33*	*25*
Sapozink et al (1986a)	*RF + RT*	*39*	*5*	*14*	*20*
Sapozink et al (1986b)	*RF + RT*	*28*	*0*	*5*	*23*
Hiraoka et al (1987)	*RF + RT*	*40*	*6*	*19*	*15*

Table 2.01. Summary of results for deep tumours

Using different response criteria, complete response rates of 10-15% and partial response rates of 20-60% are reported (Hiraoka et al., 1987; Sapozink et al., 1986a &b; Storm et al., 1982; Baker et al., 1982) Table 2.01.

Most authors reported a low incidence of minor complications such as superficial burns and fat necrosis which resolved on conservative treatment. However, in both Baker's and Sapozink's series, local pain and excessive heating of normal tissue were treatment limiting in a significant proportion of patients (up to 40%). Despite the relatively small numbers, responders in Sapozink's series were felt to have survived longer than non-responders (3 to 4 months compared 10 to 12 months). These preliminary studies demonstrate that external deep hyperthermia is a feasible technique although it is not without its limitations. Further work is necessary to improve efficacy, reduce treatment morbidity and determine more clearly what influence such therapy has on patient survival.

2.6.3 INTERSTITIAL HYPERTHERMIA

The advantages and disadvantages of this approach have been previously discussed. There are numerous uncontrolled non-randomized trials using primarily microwave and radiofrequency modes usually in combination with interstitial radiotherapy. In most instances, the tumours have been in superficial locations and have either been recurrent or unresponsive to conventional treatment. Results have indicated a high incidence of complete response ; a mean of 64% in 6 series analysed (Table 2.02).

In this table, complete regression equates with complete disappearance of the tumour while partial and non-regression denote tumour shrinkage of 75% or less and 50% or less respectively. A low incidence of serious complications is reported (Cossett et al., 1985; Emami et al., 1987, Petrovisch et al., 1989).

Interstitial hyperthermia has also been applied to deep seated malignancies within the thoracic and peritoneal cavity with mixed results. Brezovisch et al (1984) treated 6 patients with inoperable disease (5 thoracic and 1 pelvic malignancy) using radiofrequency interstitial electrodes implanted at operation. All received a course of external beam radiotherapy plus hyperthermia.

All patients showed objective evidence of tumour regression. Thoracic tumours showed no evidence of increased volume up to the time of death although the time interval from treatment to death was not stated. The pelvic tumour showed evidence of regrowth 6 months from treatment. Frazier & Corry (1984) treated 12 patients with advanced malignant disease (7 thoracic and 5 pelvic or retroperitoneal) by interstitial hyperthermia alone. The average number of treatments per patient was 13, each lasting an hour. Median survival from treatment was 6 months with all patients showing an objective response to treatment. The only complication was a small bowel perforation.

GROUP	*PATIENT NUMBERS*	*COMPLETE RESPONSE*	*PARTIAL RESPONSE*	*NO RESPONSE*
Vora et al (1982)	*16*	*11*	*1*	*4*
Oleson (1984)	*52*	*20*	*22*	*10*
Cossett et al (1985)	*23*	*19*	*4*	*0*
Puthawala et al (1985)	*43*	*37*	*6*	*0*
Emami et al (1987)	*44*	*26*	*12*	*6*
Petrovich et al (1989)	*44*	*28*	*15*	*1*

Table 2.02. Summary of results for interstitial thermo-radiotherapy

There are significant drawbacks inherent to interstitial hyperthermia. It is relatively invasive making it inappropriate as a palliative treatment when several treatments may be required. It is impractical for multiple and deeply seated tumours while post operative manipulation of electrodes and temperature thermocouples is impossible. Intraperitoneal

tumours are likely to be treated less successfully due to difficulty in encompassing the tumour volume completely, and failure to totally isolate the small bowel with risk of injury.

2.7 CONCLUSIONS

The rationale for treating human cancers using heat is based in part on anecdotal reports of complete and partial tumour regression following whole body and regional hyperthermia. There is some evidence suggesting the benefits of hyperthermia are complimentary to those of radiotherapy and chemotherapy. The wide spectrum of human tumour histology and anatomical sites mean that currently, no one single thermal technique is optimum. In general, superficial tumours (< 5 cm deep) are more successfully treated than deep ones. For the latter, conventional thermal techniques are either impractical or when feasible are invariably associated with problems. These include indifferent energy localisation with inhomogeneous temperature profiles leading to normal tissue damage and incomplete tumour treatment. Anecdotal reporting of tumour regression rates confirm indifferent results with current methods. Alternative simple thermal techniques under development such as interstitial laser hyperthermia (ILH) may have much to offer in palliating deep seated malignancies. The background and current status of ILH is discussed in the next chapter.

CHAPTER 3. REVIEW OF INTERSTITIAL LASER HYPERTHERMIA.

3.1 THE CONCEPT

The principles of interstitial laser hyperthermia (ILH) were first described by Bown (1983) using the Neodymium: Yttrium Aluminium Garnet Laser (Nd:YAG). His idea was simple and based on the properties of laser light which allows this intense and pure energy source to be transmitted down thin calibre (0.1-0.6 mm) fibre optics. Conventional laser application in medicine utilises a non-contact technique using high powers (50-80 watts) with short exposure times (2-3 seconds). The biological result (coagulation with vaporisation) in most instances is relatively crude in precision although still superior to what can be achieved using conventional energy sources such as diathermy. In addition, a significant proportion of light is reflected off the surface of the target organ; thus to reach deeper tissues, unnecessary surface damage is inflicted while it is difficult to control the depth of penetration.

Bown's idea was to insert the tip of the delivery fibre into the tissue (interstitial placement) to be treated, which is then exposed to laser light at relatively low powers (1 to 3 watts) applied for relatively long exposure times (200 to 1000 seconds). There is a precise and controlled delivery of light to the tissue which is absorbed as heat producing well defined reproducible areas of tissue necrosis centred around the fibre tip. The treated area is left *in-situ* to undergo resorption with healing by a combination of regeneration and fibrosis. Although interstitial fibre placement prevents adequate visual assessment of the results of treatment, the slow rate of energy delivery produces a biological effect whose precision and predictability are unrivalled by more conventional thermal methods. Table 3.01 compares various facets of conventional and interstitial laser application in gastroenterology.

Laser fibre tips can be delivered to almost any organ in the body. For example, hollow viscera such as the stomach and rectum can be accessed endoscopically while solid viscera such as the liver and pancreas can be reached percutaneously. Theoretically, ILH technique is more suited to solid organs as the thin calibre of fibre optics produce negligible

trauma from their mechanical insertion while healing takes place from surrounding normal tissue. The spectrum of clinical application for ILH is far reaching. Perhaps its potential for achieving accurate and safe *in-situ* necrosis of deep seated malignancies simply and atraumatically is most exciting. For it is here, in the palliation of solid organ cancers that results of conventional treatments are generally unsatisfactory. ILH may obviate the need for surgical excision, chemotherapy or radiotherapy with its attendant morbidity, mortality, costs, hospitalisation and recovery times. The implications of these benefits are likely to make such an approach attractive to both clinicians and patients

CRITERIA	*CONVENTIONAL APPLICATION*	*INTERSTITIAL APPLICATION*
Fibre Position	*Non Contact*	*Contact*
Power (Watts)	*50 to 80*	*1 to 3*
Exposure Time (Seconds))	*2 to 3*	*200 to 1000*
Biological Effect	*Coagulation & Vaporisation*	*In-situ Coagulative Necrosis*
Precision of Effect	*Moderate to low*	*High*
Treatment Assessment	*Visual*	*Monitoring modality*

TABLE 3.01. Comparison of conventional and interstitial laser application

3.2 EXPERIMENTAL WORK

This has been performed initially in normal tissues such as the liver, pancreas and colon. The nature and extent of laser mediated tissue damage, temperature gradients created, their relationship to different laser parameters and structural and functional changes in treated organs have been studied. In addition, the mechanism and time scale of healing of treated tissue and any untoward effects associated with treatment acutely and in the long term and how these relate to treatment parameters and fibre position have been evaluated. Attempts have been made to evaluate the influence of ILH on survival in animal tumour models by determining the laser parameters which equate with complete necrosis and safe healing.

Imaging is an important and complementary aspect of ILH as its biological effect cannot be reliably assessed visually. So far, US has attracted the most attention as a

potentially easy to use, cheap and simple imaging modality which does not utilise ionising radiation. Experimental work has attempted to correlate real time and end treatment images with macroscopic and microscopic extent of tissue necrosis. Clearly, such studies are fundamental to the successful clinical application of ILH. Other workers have pursued the technical aspects of laser delivery systems, especially fibre tip design inorder to maximise the biological effect of ILH for a given treatment energy. It is this aspect of experimental work I shall start with before going on to consider specific organs.

3.2.1 DELIVERY SYSTEMS

Interstitial laser light delivery systems have been investigated using 3 main fibre types. A bare fibre optic, where the plastic cladding has been removed exposing the light transmitting quartz or glass fibre is the simplest arrangement. An alternative is to use diffuser fibres which in theory provide more uniform light irradiation of the tissue producing a more homogeneous biological effect. Lastly, the versatility of sapphire tips which can be coupled to a bare quartz fibre has attracted a lot of attention. The tip geometry can be selected to enhance a particular biological effect such as cutting or coagulation.

Van Eeden (1988) investigated variation in maximum extent of necrosis in liver. Using a bare quartz fibre, he altered the fibre diameter, fibre tip configuration and depth of entry of laser light both in-vitro and in-vivo. Comparison between 400 and 600 micron quartz fibres for a given treatment energy produced no significant difference in the extent of necrosis. Altering the fibre tip of a bare 600 micron fibre by etching the tip with hydrofluoric acid (a simple diffuser effect is produced), or attaching a sapphire probe did not produce a useful benefit over simple cleavage and removal of the plastic cladding. It was noted that the optimum depth for maximum thermal necrosis in vivo and in vitro for a given treatment energy is 5 to 10 mm.

Hashimoto et al (1985), in a clinical feasibility study treated patients with liver cancer using powers of 5 to 15 watts from a Nd:YAG laser coupled to a laser fibre with a modified quartz diffuser tip. Preliminary results indicate successful induction of tumour necrosis although the extent of necrosis is not specified. While allowing more uniform tissue irradiation, the power density from a diffuser fibre is likely to be low at the tip-tissue

interface. This may prevent tissue carbonization due to excessive temperatures around the fibre tip. However, power densities maybe insufficient for adequate coagulation of large tissue volumes. In most instances, self heating of the diffusing microdome limits laser powers to only 1 watt.

Sapphire tips are widely used in a variety of clinical laser applications. Their attraction stems from geometric modifications made to the sapphire to tailor the power density to a desired biological effect. Using a chiselled probe generates very high power densities at the tip with very little scattering into non-targeted tissues. This allows very precise tissue cutting. A broader sapphire tip lowers the power density considerably due to increased interaction surface area. As a result, the predominant biological effect is coagulation. However, Sapphire tips are not without their problems. Using an end on and an integrated sphere power meter, Steger et al (1988) demonstrated a 30-50% loss of the input power at the sapphire tip. Direct thermometery demonstrated a 50 to 60^{o}C rise at the junction of the proximal sapphire end and metal connector compared to its distal end. A plausible explanation is that a proportion of laser light is probably reflected back from the proximal sapphire surface to be absorbed by the metal connector causing it to heat up. A third to one half of the input laser energy contributes to this effect and, in essence, makes the sapphire tip act more like a hot probe rendering the biological effect less predictable. This phenomenon has two undesirable effects. For equivalent laser energies, the diameter of necrosis using a sapphire tip is significantly smaller than with a bare fibre while co-axial water or gas is needed to cool the collar assembly. Fatal air emboli have been associated with gas cooling during gynaecological procedures following inadvertent entry of air into a vein. In addition, the width of sapphire tips and the metal collar required to fix them to the laser fibre makes them impractical for percutaneous use.

The low powers necessary for ILH mean prolonged treatment times when treating large tissue volumes. The logical answer is to attempt to increase the laser power, however, diffusing quartz fibres and sapphire probes are unsuitable for high power photocoagulation. In an attempt to overcome this problem, Godlewski (1988) developed a device for inducing deep focal tissue necrosis and vaporisation using a Nd:YAG laser at high powers (100 Watts). This consisted of a large proximal base attached to an axial

channel which allows the passage of a laser fibre with two lateral ducts for a cooling circuit. Within the axial channel, a disposable sheath (200 mm long with a diameter of 5 mm) which houses the bare fibre and cooling circuit. The distal end of the sheath is closed by a window through which the laser beam is transmitted. The window and fibre are cooled by circulating water. This device was used at laparotomy on porcine liver with a 6 mm trocar to allow the device to be introduced into the liver substance. Treatment parameters consisted of ten 1 second exposures at a power of 100 Watts. One hour from treatment, ultrasound examination revealed a central echo free area corresponding to the central charred cavity with a circumferential hyperechoeic pattern denoting necrotic but non-vaporised tissue. By the third to tenth day, these features were well demonstrated, in addition, a further hypoechogenic halo of oedema gave a characteristic bull's eye appearance. Post mortem analysis 3 days from treatment showed a well defined spherical area of tissue necrosis up to 18 mm in diameter (range 12 to 18 mm) with a central zone of cavitation and charring 5 to 8 mm in diameter. The animals showed no ill effects from their treatment with all treated sites healing by scarring within 4 months from treatment. However, at no stage was any attempt made to correlate the ultrasound assessment and post mortem evaluation of the extent of necrosis nor study the effect of lower laser powers on the extent of necrosis. A major drawback to this approach is the rapidity of energy delivery and ensuing biological effect making it impossible to study the evolution of thermal changes in real time. Sonographic assessment of the biological effect can only be made once the damage is done be it to targeted or non-targeted tissue. This makes for poor control of the extent of tissue necrosis with possible inadvertent tissue damage. Clearly, the dimensions of Godlewski's device make impractical for percutaneous use. If this technique is to offer any useful advance, a compromise has to be made between short exposure times / high powers and control over the biological effect.

Sophisticated delivery systems which monitor temperature and light distribution during laser photocoagulation have been reported. Daikuzono and his colleagues (1988) developed a new computer controlled Nd:YAG system which interfaces with temperature probes placed within the treated tissue. This is more fully discussed later in this chapter.

Almost all reports in the field of laser hyperthermia have utilised single laser fibres with or without modification. The concept of a multi fibre delivery system is theoretically an attractive one allowing a single laser to simultaneously produce clinically useful powers of equal intensity down 2 or more fibres. This topic is further discussed in the next section.

3.2.2 ORGAN STUDIES

I) LIVER

Matthewson et al (1987) provided some of the best documented results on ILH using much lower powers than Godlewski. The experimental model consisted of exposing the left lobe of the rat liver at laparotomy which was irradiated using a single 400 micron diameter fibre inserted interstitially. The liver was photocoagulated using a range of laser powers (0.5 to 2.0 watts) from a Nd:YAG laser with varying exposure times (100 to 1000 seconds). The animals were killed 3 to 4 days from treatment to evaluate the extent of necrosis. The results allowed the following conclusions to be made.

1. Well defined areas of necrosis, roughly spherical in shape and up to 16 mm in diameter were produced.
2. The diameter of the extent of necrosis depended on the laser parameters used. The same laser parameters produced reproducible lesions.
3. The extent of necrosis was at its maximum on the 7th post treatment day.
4. Treatment energy greater than 1000 joules did not increase the diameter of the necrotic area.
5. Post mortem angiography of the treated area showed total obliteration of vessels up to 1.5 mm in diameter at powers of 1.0 watts and above.

Mean steady temperatures at the fibre tip were $100^{o}C$ at 2.0 watts while at 8 mm from the tip the equivalent reading was $52^{o}C$. Compared to Godlewski high power approach which produced extensive cavitation and carbonization, histological examination of the liver four days from treatment showed a small central area of cavitation with charring. Around this was a well defined zone of coagulative necrosis associated with an acute cellular infiltrate. All lesions healed by regeneration and fibrosis leaving a small central scar within 60 days from treatment. Light transmission through the liver during

treatment fell by up to 75% of its initial level supporting the conclusion that the optical properties of the liver change during treatment particularly at high power settings (≥ 1.5 watts). Interestingly, for equivalent energy inputs, the diameter of the zone of necrosis did not vary if a continuous or pulsed laser was used.

The volume of necrosis produced using a single fibre is too small for useful clinical application. A multi fibre system with its inherent advantages of more uniform tissue illumination, large necrosis volumes produced at relatively short cumulative exposure times is an attractive proposition. Steger et al (1992) have carried out work using a multi delivery system consisting of four fibres in canine liver. At laparotomy, the fibres were positioned in juxtaposition under ultrasound control with a separation of about 15 mm between individual fibres. Using a power output of 1.5 watts per fibre applied for 670 seconds, the liver was photocoagulated. Thermocouples positioned in the centre of the treatment zone showed an area of thermal overlap with temperatures of 55 to 65^{o}C at 500 seconds. All treatments were associated with rises in serum Aspartate transaminase the extent of which roughly correlated with the extent of necrosis. Titres returned to normal by 60 days from treatment. Despite this, no animal developed any untoward effects following treatment. At one week, well defined spherical areas of confluent necrosis up to 3.5 cm in diameter were seen centred around the fibre tips. The evolution of such areas was well delineated in real time using intra-operative ultrasound with good correlation between the sonographic and pathological extent and nature of the immediate post treatment changes. Similarly, subsequent regression of the necrotic zone up to 3 months from treatment were well demonstrated. Histological follow up at 6 to 7 months showed of 18 treatment areas, 17 had healed completely and safely leaving a small central scar with no systemic upset to the animal. Sepsis developed in one treated area due to a recognised lapse in aseptic technique.

Dachman et al (1990) expanded on Matthewson's single fibre studies using a percutaneous approach to place a single fibre in porcine liver under ultrasound guidance. A Nd:YAG laser was fired continuously for 360 seconds at a power of 1 to 4 watts with sonographic monitoring of the evolving thermal changes. By comparing the sonographic images with naked eye appearances of the treated areas, distinction between two major sonographic patterns was noted. Four to eleven days from treatment, ultrasound showed a

4 layered bull's eye. This consisted of a central hypoechoeic area representing the carbonised cavity surrounded by a hyperechogenic halo corresponding histologically to an area of dense coagulum. Beyond this lay a circumferential hypoechoeic area representing coagulative necrosis of liver tissue with the last hyperechoeic zone separating the treated area from normal liver. The second sonographic pattern was noted three to seven weeks from treatment consisting of an echogenic area with or without a central cavity. Histologically, this consisted primarily of dense connective tissue.

Dachman's sonographic-pathological assessment of laser mediated interstitial hyperthermia in the liver corresponds closely with the intra-operative sonographic images obtained by Steger et al (1992) in canine liver using multiple fibres inserted at laparotomy and by Bosman et al (1991) in porcine liver using transabdominal ultrasound following percutaneous single fibre insertion. Dachman and Bosman's work would suggest that it is feasible to insert laser fibres percutaneously into the liver with relative precision under ultrasound guidance; in addition, it provides a relatively reliable monitoring modality to visualise evolving, final and healing changes within treated areas in the normal liver.

Some workers regard lasers as expensive, unreliable predominantly research orientated tools whose role could be fulfilled, in part, by much simpler and cheaper interstitial modalities such as alcohol injection. In a post mortem study performed in porcine liver two days following treatment, the biological effect of percutaneous alcohol injection was compared with percutaneous interstitial Nd:YAG therapy (Van Eyken et al 1991). Unlike the well defined predictable lesions produced by the laser, interstitial alcohol therapy produces irregularly shaped, poorly cicumscribed lesions. Their extent was unpredictable and invariably extended along the injection tract and adjacent centrilobular and portal veins. These features are attributable to inhomogeneous alcohol distribution in the tissues as it tends to pass along planes of least resistance. The peritoneal cavity of those animals treated using alcohol contained a haemorrhagic sero-sanguinous fluid almost certainly due to retrograde flow of alcohol along the needle tract. It would seem that the advantage of the laser over alcohol is a real and useful one.

II) PROSTATE

A similar dose response relationship to that seen in the liver has been demonstrated by McNicholas and his colleagues (1988) in canine prostate using low power interstitial Nd:YAG laser energy (1.0 to 2.0 watts). A close correlation exists between input energy and diameter of necrosis induced using single and multiple fibres. Single fibre placement at a power of 1.5 watts for 500 seconds produced an area of necrosis of 14 mm in diameter increasing to 26 mm using 2 fibres. Cystic degeneration of the treated areas occurred with healing by resorption and fibrosis within 60 days from treatment. Of 17 animals treated, there was a single case of urethral fistula indicating the importance of careful needle positioning. Disappointedly, trans-rectal ultrasound failed to demonstrate the necrotic areas which were subsequently confirmed at post mortem.

III) PANCREAS

Interstitial laser therapy has also been applied experimentally to the canine pancreas using single and multiple fibres coupled to a Nd:YAG laser (Steger et al., 1987). As for the liver, precision and predictability of the extent of necrosis depended upon the laser input energy. However, in contrast to the liver, the margin between predictable safe tissue necrosis and precipitating fatal structural organ damage was small and depended on the two factors. Using the pancreatic duct to position the laser fibre resulted in duct rupture during photocoagulation with an leakage of exocrine secretions leading to a fatal haemorrhagic pancreatitis. In addition, excessive laser powers ($\geq$ 2.0 watts) using a single fibre produced a similar result. Single fibre powers of 1.0 watts or four fibres inserted in juxtaposition and fired simultaneously at a power of 1.0 watts for 1000 seconds produced safe areas of tissue necrosis measuring 1.7 and 4 cm respectively. Healing occurred predominantly by fibrosis at one month from treatment. All treatments were associated with rises in the serum amylase which returned to normal 2 to 4 weeks from treatment. However, this was not associated with deterioration in the condition of any of the treated animals. Fears of fistula or abscess formation have not been realised. The suggestion from this work was once the appropriate laser parameters were defined, ILH could be applied effectively and safely to the pancreas.

IV) COLON

On a theoretical basis, hollow organs may be less forgiving to the thermal effects of interstitial laser therapy as there is less normal tissue margin around potential treatment sites. However, if gentle and carefully controlled necrosis were to be possible, then this may prove clinically beneficial, for example, malignant or benign sessile polyps in patients unfit for surgery. Matthewson et al (1988) compared the tissue response of normal colon and Dimethyl-hydrazine induced colonic cancers in rats. Normal tissue, as expected proved vulnerable. With the laser fibre just touching mucosa, 1 watt for 75 to 100 seconds caused transmural necrosis with a significant reduction in mechanical strength of the colon for the first seven days from treatment as assessed by bursting pressure studies. Healing occurred over 3 weeks with a small amount of fibrosis but no luminal stenosis. Over treatment of experimental tumours produced colonic perforation while under treatment left residual viable tumour. However, once the appropriate laser parameters were defined, complete tumour necrosis occurred leaving a shallow ulcer which healed completely and safely within 4 weeks from treatment.

V) SUBCUTANEOUS TUMOURS

The influence of interstitial laser therapy on the behaviour of transplantable subcutaneous tumours have been studied by Matthewson et al (1989) and Sweetland et al (1990) independently using a Nd:YAG laser. Both workers treated an aggressive rapidly growing fibrosarcoma of a fixed diameter (1.0-1.5 cm) and were able to demonstrate worthwhile partial tumour regression compared to controls. In those animals where the laser parameters were matched to the extent of tumour under treatment then total tumour necrosis was achieved with complete and safe healing. Indeed, in Matthewson's study, local recurrence and survival rates rates were superior in the laser treated group compared with a similar surgically treated group.

Reliable visual assessment of the effects of interstitial laser therapy cannot be made for several reasons. Deeply seated intraperitoneal organs where fibre placement is performed percutaneously are not accessible for inspection. Even superficial tumours do not lend themselves easily to inspection of the biological effect due to interstitial fibre

placement. Ultrasound fulfils the role of a simple, non-invasive monitoring modality particularly suited to visualising deeply seated solid organs in the peritoneal cavity. However, alternative invasive monitoring modalities have been investigated. Sophisticated systems which monitor changes in light transmission and temperatures within tissues have been reported. Transmission of laser light alters as the optical properties of the tissue change with treatment. In addition, thermally mediated necrosis depends upon temperature levels attained and the duration that temperature is maintained. These factors may provide a means of real time treatment monitoring. Daikuzono and his colleagues (1988) used a new computer controlled Nd:YAG system to produce interstitial hyperthermia. Continuously monitoring temperature sensors were placed directly into the target tissue with a computer programme interfacing with the laser and temperature probes used. If the temperature at the sensing probe fell or rose beyond definable limits, the laser output adjusted accordingly to restore the temperature to the desired level. In this way it becomes possible to maintain a steady temperature within a known tissue volume over prolonged periods with a high degree of precision. The disadvantage of temperature and light sensing probes is that they are invasive and therefore are impractical for multiple and deeply seated tumours. In addition, they only provide a 'point' assessment. That is the information provided is only relevant to the area sampled and does not necessarily reflect what is happening elsewhere within the treatment volume. Inhomogeneity in tumour blood flow is likely to produce variation in temperatures leading to 'hot' and 'cold' spots. 'Hot' spots represent over treatment which is unlikely to be clinically significant in organs with large functional reserves such as the liver. On the other hand, 'cold' spots may go undetected due to non-sampling purely occurring as a chance happening. While the probability of this happening can be reduced by using more probes, physical constraints will limit numbers.

3.2.3 MECHANISM OF INTERSTITIAL LASER HYPERTHERMIA

Using thermal camera images, thermocouple measurements, optical penetration calculations and ultrasound images in-vivo and in-vitro, Steger (1990) proposed a plausible sequence of events when Nd:YAG laser light interacts interstitially with tissue. Mechanical introduction of a fibre optic inevitably damages capillaries at the insertion site releasing

blood. Upon activation of the laser, light transmitted from the fibre end heats the thin blood film to a temperature of 50 to 60 ^{o}C forming an envelope around the fibre tip. Continued heating causes boiling and evaporation of solutes and solvents leading to a rise in pressure within the envelope which ruptures. These series of events are complete within 30 to 50 seconds of irradiation. By then, there will be penetration and scattering of laser light into the tissues causing blood and tissue protein coagulation and charring. The dark nature of the char almost completely absorbs the infrared light with an associated rise in temperature. The laser fibre tip and the surrounding char then act as a point heat source with thermal diffusion into adjacent tissue.

Whether such a sequence occurs in relatively avascular non-pigmented tissue such as liver metastases must be open to question. It is interesting to note that real time sonographic changes seen clinically in the treatment of liver tumours are remarkably similar to those observed in normal liver studies in animals.

3.3 CLINICAL STUDIES

There has been little work carried out using interstitial laser therapy. Reports have come from non-randomized uncontrolled studies in small patient groups with advanced malignant disease unresponsive to conventional treatments. The focus of interest has centred on treating solid organ tumours, in particular the liver. These phase I studies have provided encouraging results and raised questions which have provided the impetus for further research in this expanding field.

The first reported clinical work on ILH for liver tumours came from Hashimoto and his colleagues (1985) in Japan. Ten patients, two with hepato-cellular carcinoma (diameter 3 & 5 cm) and eight with colorectal hepatic metastases were treated at laparotomy using a modified diffusing quartz fibre which was positioned into the tumours under ultrasound guidance. A continuous output of 5 watts from a Nd:YAG laser was applied until all hypoechogenic areas of tumour were converted to hyperechogenic patterns on sonographic monitoring. The alpha feto-protein levels fell to normal levels within 3 months of treatment while the metastatic tumours showed similar dramatic falls in the carcino-embryonic antigen titres indicating successful induction of tumour necrosis. There were no complications but

no assessment was made of the extent of necrosis or the long term influence of treatment on patient survival. Adopting a similar 'open' technique to that used by Hashimoto, Schroder and Hahl (1989) treated four patients with advanced malignant disease of the liver. All patients showed radiological and cytological evidence of tumour necrosis within 2 weeks from treatment. Unfortunately, one patient developed an infection in a laser induced area of necrosis while another died from an air embolus originating from coaxial gas used to cool the sapphire tip on the laser fibre (schroder et al., 1989).

A more recent paper by Huang and his colleagues (1991) reported their results using ILH in 5 patients with 7 inoperable hepato-cellular carcinoma measuring 4 cm or less. The procedure was performed percutaneously using a hybrid probe inserted into the tumour centre under ultrasound control. The probe consisted of a 400 micron diffusing quartz fibre incorporating a thermocouple. A Nd:YAG laser was preset at 2 to 3 watts to achieve a steady state temperature of 43 to 45 ^{o}C for at least 20 minutes. The procedure was well tolerated in all patients. Immediately following treatment, all tumours showed increased echogenicity on ultrasound similar to that seen in experimental normal liver studies of Steger and Dachman. Follow up computerised tomography revealed evidence of necrosis in all tumours while biopsy in 6 confirmed tumour necrosis with viable tumour in only one.

The only published report on clinical application of interstitial laser therapy in hollow viscera has come from Barr and his colleagues (1989). Three patients with large inoperable friable bleeding cancers of the stomach unresponsive to conventional high power YAG application were treated. An artificial sapphire probe was inserted into different regions of the tumour through the biopsy channel of a gastroscope. The tumours were treated using a Nd:YAG laser at a power of 1 to 5 watts for 200 to 1000 seconds. Assessment of treatment was purely visual and therefore probably overestimated the true extent of tumour necrosis achieved. All patients showed dramatic reductions in their transfusion requirements until death (mean follow up of 21 weeks). While uncontrolled, this small study illustrates a further benefit of ILH when conventional therapy is either exhausted or inappropriate.

3.4 CONCLUSIONS

To-date, experimental work in normal liver, pancreas, prostate and colon of animals has confirmed the feasibility and safety of ILH in producing tissue necrosis. Animal tumour model studies have shown that once the laser parameters are matched to tumour volume under treatment, successful and safe tumour eradication can be achieved.

Preliminary clinical studies using an open approach for fibre placement in liver tumours have demonstrated the potential of ILH. Radiological, histological and tumour marker measurement have confirmed successful tumour necrosis with minimal complications.

Chapter 4 considers the logical progression of work carried out on ILH so far as a basis for this thesis.

CHAPTER 4. AIMS OF THESIS.

An overview of the current experimental and clinical status of ILH has already been presented in chapter 3. As a consequence, three specific topics have been identified for research and form the basis of this thesis. The rationale and potential benefit of each topic is considered below.

4.1 SOLID ORGAN TUMOURS

4.1.1 LIVER CANCER

Experimentally, ILH in normal animal liver using single and multiple fibre systems at laparotomy have produced well defined reproducible tissue necrosis which heal safely. The evolving, final extent and subsequent regression of the zone of necrosis can be reliably followed using ultrasound (Steger et al., 1992). Similar results have been demonstrated using ILH percutaneously in normal liver in animal models. Relatively accurate percutaneous fibre placement is possible using ultrasound guidance. In addition, ultrasound applied more conventionally across the abdominal wall remains an effective real time monitoring modality in delineating tissue changes at the fibre tip (Bosman et al., 1991; Dachman et al., 1990).

Ideally, the next step would be a liver tumour model to establish whether data derived from normal liver studies can be reproduced in a tumour model given its different optical characteristics. However, liver tumour models in small animals are unreliable and difficult to work with while large animal tumour models do not exist. At any rate, Home Office animal licence regulations do not permit large animal tumour models. Although theoretically desirable, the impetus to perform this work has been lost to a certain extent with the report of phase I studies published by Hashimoto et al (1985) and Schroder et al (1989) using ILH to treat primary and secondary liver cancer in patients.

Liver cancer is a common clinical problem world-wide. To assess the potential impact of ILH (or any new treatment), the natural history, success and shortcomings of conventional therapy requires evaluation. To this end and commensurate with its prevalence, chapter 5 is devoted to the natural history, detection and treatment of liver

cancer. Identifying the drawbacks of conventional treatments, when taken with the properties of ILH, allows identification of a subset of patients with liver cancer who may benefit from laser therapy.

The rationale for ILH therapy is simple. Liver cancer is a uniformly fatal condition if untreated. The palliative management of this common condition is on the whole unsatisfactory. Survival is clearly related to the extent of hepatic replacement by tumour. If ILH proves to be a feasible and safe technique for reducing viable tumour burden, then it may offer a useful palliative role for achieving local tumour control with possible survival benefits.

Preliminary work by Hashimoto (1985) and Schroder (1989) and their colleagues independently in small number of patients with liver cancer have illustrated that ILH is a feasible technique for inducing *in-situ* tumour necrosis. However, both groups of workers subjected their patients to a laparotomy to position the laser fibres. Given the palliative nature of ILH, an operative approach seems rather harsh and not without risk to the patient. This makes the technique invasive, excludes patients unfit for general anaesthesia and makes retreatment of those who relapse impractical. In addition, relatively long hospitalisation and recovery times with its attendant costs and effect on survival time quality make the open approach unattractive. If reliable tumour necrosis could be achieved safely using percutaneous fibre placement then the advantages over an open approach would be significant.

Percutaneous biopsy of hepatic lesions using ultrasound and CT guidance is a common and relatively safe technique. In the light of this, percutaneous multiple fibre placement using a similar approach would seem to be perfectly possible. The question is whether percutaneous multiple fibres can be inserted with sufficient precision into a relatively small target area under ultrasound guidance ? If so, is percutaneous ILH therapy a feasible technique for inducing necrosis in hepatic tumours and can this be achieved safely ? The work in chapter 6 set out to answer these questions.

4.1.2 PANCREATIC CANCER

Compared to the liver, relatively little work has been done in normal animal pancreas using ILH. Available data has shown that single and multiple fibre treatments produce similar results to those seen in the liver (Steger et al., 1987). However, the margin between safe tissue necrosis and fatal organ damage is much smaller in the pancreas given its relatively small size, complex retroperitoneal site with many adjacent vital structures. This emphasizes the importance of optimum fibre placement and careful selection of laser parameters.

Despite the existence of an animal tumour model for pancreatic cancer (Syrian Golden hamster), as yet, there is no reliable data on the effect of ILH on pancreatic tumour. Admittedly, the model is difficult. Induction times are long requiring frequent injections of a highly potent carcinogen. Tumour yield is unpredictable with a preponderance of multifocal pancreatic tumours within a small organ. In addition, extra-pancreatic tumours are common limiting the usefulness of the model. Therefore, a phase I clinical feasibility study is the next reasonable step forward.

The incidence of pancreatic cancer has risen significantly in the last 50 years. In 20% of patients surgical resection is feasible. A further 30% have unresectable locally confined tumours and the remaining 50% have metastatic spread. Thus, 80% of patients are suitable only for palliative treatment which is increasingly non-surgical. However, rarely is there any attempt to control local tumour growth. Those techniques available are discussed in chapter 7 and can be summarised as effective but invasive with complex treatment regimens which are associated with a significant morbidity. On the premise that local tumour control may translate to a useful gain in survival, it seems reasonable to offer patients with apparently localized but unresectable pancreatic cancer treatment to retard tumour growth. This approach is only acceptable if treatment is non-invasive and safe.

Chapter 7 reports the results and complications of the first feasibility study using ILH percutaneously to debulk apparently localised pancreatic cancer in 5 patients. The future role of the technique is discussed.

4.1.3 BREAST CANCER

Breast cancer remains the commonest malignant disease in woman. Increasing public awareness, self examination and an active national screening programme has produced an increase in the number of clinically early palpable and impalpable cancers.

The trend towards conservative surgery with good results for selected localised breast cancer has generally gained wide acceptance amongst surgeons. In theory, it may be possible to avoid surgery completely by tumour destruction within the breast. If the extent of laser mediated necrosis could be matched accurately to tumour volume, then ILH could achieve this goal with minimal or no scarring. The physical and psychological morbidity of surgery could thus be avoided to the potential benefit of the patient. An extension of this idea would be to treat patients who refuse surgery or develop recurrent disease following aggressive medical treatment for inoperable carcinoma. Fungation, bleeding and pain due to uncontrolled local tumour growth could therefore be avoided. Ultimately, ILH could be employed to treat *in-situ* and early invasive breast cancer where the probability of axillary nodal disease is low.

To date, there is no data on the effect of ILH on normal breast tissue in animals or humans. Dose response relationship, mechanism and time scale of healing and the usefulness of ultrasound for fibre placement and treatment monitoring are unknown. However, data is available from animal tumour models of subcutaneously transplanted tumours (Matthewson et al., 1989; Sweetland et al., 1990). This may serve as an approximate model for breast cancer. Results have shown that once the appropriate laser parameters are defined and related to tumour volume, complete tumour necrosis can be achieved with minimal scarring.

Given these results, it seems reasonable to proceed to a clinical feasibility study treating patients with apparently localised breast cancer using ILH with percutaneous fibre placement under ultrasound control. The experimental nature of this work means it cannot be justified ethically to treat patients with potentially early and therefore curable disease with ILH alone. However, it is possible to evaluate ILH in patients with operable disease destined for surgical excision by treating them at various time intervals prior to tumour

resection. The operative specimen can then analysed histologically correlating the extent of laser mediated necrosis with the laser parameters used. This work is presented in chapter 7.

4.2 LASER TISSUE INTERACTION

Good experimental data on the effect of ILH in normal liver has been provided by several workers (Matthewson et al., 1987; Dachman et al., 1990; Steger et al., 1992; Bosman et al., 1991). For reasons previously discussed, no such data is available for liver tumours.

An important question posed by the paucity of tumour work is whether data obtained from normal liver studies can be reliably extrapolated when treating hepatic tumours in a clinical setting. More specifically, are laser parameters derived from normal tissue studies optimum for inducing necrosis in hepatic tumours and secondly, are sonographic images accurately depicting evolving and final extent of necrosis in normal liver equally valid as reliable markers of tumour necrosis ?

These questions arise because laser tissue interaction is highly dependant on the optical properties of the treated tissue. Normal liver parenchyma is highly vascular and heavily pigmented thus varying significantly in its optical characteristics from its malignant counterpart. This question is relevant due to the relatively poor absorption of the Nd:YAG wavelength (1064 nm, near infra red) which means that its biological effect is highly dependant on scattering to increase the volume of treated tissue. Pigmented tissue (normal liver) is a much better scatterer of the near infra red wavelength than non-pigmented tissue (tumour) which will transmit a higher proportion of the incident laser light. On a theoretical basis at least, it seems unlikely that optimum laser parameters derived from normal liver studies are likely to be equally effective for hepatic tumours.

Resolving this question is not easy. Large animal tumour models are not readily available and smaller animal models are difficult to work with since it is not easy to produce discrete tumours in the liver. An alternative approach is to treat patients with hepatic metastases destined for hepatic resection prior to surgery. The surgical specimen can then assessed and the extent of laser mediated necrosis correlated with the laser parameters used and the sonographic and CT images obtained. However, this is difficult to justify ethically

as the patient does not derive any obvious benefit from what maybe a hazardous procedure with the potential for tumour dissemination.

It is relatively easy to produce solitary discrete tumours in subcutaneous sites (Matthewson et al., 1989). Treating such an acellular tumour with comparable laser parameters used in the liver and then comparing the extent of necrosis in both would be useful. Even allowing for different anatomical locations with its implication on relative blood supply and patterns of healing, this would provide some insight into the practical significance of tissue optical characteristics on the extent of necrosis. Matthewson and his colleagues (1989) treated well defined transplanted subcutaneous tumours using ILH with a Nd:YAG laser. Once the appropriate laser parameters had been identified, he was able to achieve complete tumour necrosis. However, the work suffered from several problems. Tumour dimensions were not standardised with variations up to 50% for given laser parameters. No account was made for spontaneous degeneration, a relatively common event with transplanted tumours which are invariably biologically aggressive with rapid doubling times. lastly, the laser parameters used by Matthewson were not comparable to those used in normal liver studies.

The work in chapter 9 addresses these problems by standardising tumour dimensions, excluding spontaneous necrosis and using laser parameters comparable to those used in Matthewson's liver study (1987). By comparing the extent of necrosis in subcutaneous tumours with rodent liver for comparable laser parameters, then some inference can be made on the relative influence of tissue optical features on the extent of necrosis.

4.3 MONITORING

The maximum benefit of ILH can only be safely derived by fully identifying the limits of the pathological tissue under treatment then matching the extent of laser mediated necrosis to it. Imaging forms a critical component of the concept of accurate and precise tumour necrosis.

For solid intraperitoneal organs such as the liver, ultrasound and computerised tomography are the current imaging modalities of choice. However, there is a paucity of

good data correlating the radiological and true pathological extent of hepatic tumours as measured in operative specimens or at post mortem. Secondly, as yet, there are no studies correlating real time sonographic changes in hepatic tumours during and following ILH with the true extent of tumour necrosis. Work is required to determine the correlation between the extent of necrosis seen on CT following ILH with the histological extent of tumour necrosis. Lastly, despite advances in US and CT techniques and equipment, it is not always possible to identify the peripheral limits of hepatic tumours with absolute precision especially following preliminary laser treatment.

Therefore a need exists for improved precision in interpreting the fate of hepatic and other tumours during and following treatment. An alternative non-radiological approach to achieve this is to use invasive probes which monitor changes in either temperature, oxygen tension, transmission of laser light or blood flow at the treatment site. Such an approach is likely to have a complimentary role to conventional imaging rather than replace it entirely. The probes could be placed percutaneously at points at highest risk of incomplete treatment such as areas furthest away from the laser fibre. Alternatively, they maybe placed near major blood vessels where rapid blood flow may act as a heat sink minimising the biological effect with an increased risk of incomplete treatment. Major biliary radicles are sensitive to thermal injury. Tumours at or near a major bile duct could be treated more safely and completely using one or more probes placed strategically.

Experimental data (Matthewson et al., 1987) has demonstrated obliteration of blood vessels within the necrotic zone following ILH in rat liver. It would seem a reasonable assumption that a simple technique to assess changes in blood flow at a treatment site during photocoagulation would be useful to assess tissue viability. Laser doppler flowmetery provides a real time quantitative assessment of microcirculatory blood flow. If to be of any clinical value, it is essential to identify what relative fall in blood flow equates with irreversible tissue damage. The work in chapter 10 evaluates whether laser doppler flowmetery is an effective technique for reliable real time evaluation of rat liver viability during ILH therapy.

CHAPTER 5. LIVER CANCER

5.1 NATURAL HISTORY

Liver cancer is a common problem worldwide and continues to pose a therapeutic dilemma. In western clinical practice, the commonest pattern of involvement is metastatic infiltration and outnumbers primary cancers by 50 to 1 (Pickren et al., 1982). With the exception of lymph nodes, the liver is the commonest site for secondary malignant tumours. It is estimated that 40% of adult patients with primary extrahepatic malignant disease who come to autopsy have hepatic metastases (comparable figure for the lung is 30%). The five commonest primary sites responsible for liver metastases are, in descending order of frequency, bronchus, colon, pancreas, breast and stomach. It is worth noting that in only 2.5% of patients with metastatic disease is the liver the sole site and such cases occur mainly in tumours drained by the portal circulation (Cadey., 1983). Of these tumours, 50% give rise to hepatic metastases with colorectal cancer numerically the commonest primary.

The most important determinants of survival from hepatic metastases are :

1. The extent of hepatic involvement.
2. Presence or absence of extrahepatic disease.
3. Uncontrolled locoregional disease.
4. Anatomical / histological type of the primary tumour.

There are several important caveats to survival times which need to be borne in mind. Understandably, almost all survival figures are drawn form retrospective series, since controlled trials with a non-treatment arm cannot be ethically justified. Meaningful retrospective data analysis is limited by non-documentation or non-standard assessment of the four most important determinants of survival mentioned above. To overcome this, Pettaval et al (1984) suggested a staging system based upon the percentage hepatic replacement index of liver parenchyma by tumour

Stage I - < 25% replacement.

Stage II - 25 - 75% replacement.

Stage III - > 75% replacement.

Accurate staging using this system requires several imaging techniques, each likely to harbour an inherent tendency to over or underestimate the extent of involvement. Similarly, comparison within different series assumes identical imaging modalities using comparable techniques. A second important phenomenon in interpreting survival figures is 'lead time bias'; that is reported survival of liver tumours depends on the point in their natural history at which they are detected. For example, modern CT imaging techniques can detect 1 cm tumours while 20 years ago a similar tumour could only have been detected by isotope scan at a diameter of 2 cm or more. Thirty years ago, the diagnosis could only have been achieved when the patient became symptomatic. A recorded survival of 2 years, 1 year and 3 months respectively could have been documented. Another consideration is 'stage bias'. To-days increasingly sensitive staging techniques tend to upgrade the extent of a patient's disease at the time of diagnosis. Thus a patient who would have previously been considered not to have hepatic metastases would have tumour detected there by modern imaging modalities. These considerations allow only the broadest generalisations to be made from the literature.

Jaffe et al (1968) reported a detailed study of factors influencing survival in 390 patients with hepatic metastases from a variety of gastrointestinal cancers. Survival was assessed from diagnosis and complete follow up was possible in all patients. There was a very striking linear relationship between percentage survival and log survival time, with 50% survival at 75 days, only 7% at 1 year and less than 1% at 2 years. Factors significantly influencing survival were primary site with colorectal tumours faring better than stomach, pancreas or biliary tract. Similarly, the extent of hepatic involvement and histological tumour type were important with adenocarcinoma having a better prognosis.

Available evidence would suggest that removal of the primary tumour will improve prognosis as well as provide superior palliation (Oxley & Ellis., 1969). In a prospective study of patients with liver metastases from tumours of the colon or rectum, the one year survival rate for patients who had primary tumour resection was 32% compared to only 15% in those who did not. The decision not to resect may have reflected advanced local disease, nevertheless, the evidence is in favour of removing the primary tumour whenever possible (Wanebo et al., 1978).

Colorectal hepatic metastases are a common clinical problem and deserve a specific mention as the natural history and influence of therapy has been best studied in this group. Approximately 20% of patients with colorectal cancer have hepatic metastases at the time of diagnosis with a further 30% developing overt metastases 2 to 3 years following an apparently curative resection. Untreated, the prognosis is poor with most patients dead within 2 years from diagnosis (Wood et al., 1976). Most reported series are retrospective and cite an average survival from diagnosis of less than 7 months (Flanagan & Foster., 1967, Oxley & Ellis., 1969, Bengmark & Haefstrom., 1969, Wood et al., 1976).

In reported series, it would seem clear that survival is closely related to the extent of hepatic involvement by tumour (Table 5.01).

REFERENCE	*EXTENT OF HEPATIC INVOLVEMENT*	*MEDIAN SURVIVAL (months)*
NIELSON ET AL (1971) †	*FEW*	*18*
	MULTIPLE	*5*
BENGTSSON ET AL (1981) †	*< 25 %*	*6.2*
	≥ 75 %	*3.4*
GOSLIN ET AL (1982)	*≤ 3 METS*	*24*
	≥ 4 METS	*10*
WAGNER ET AL (1984)	*SOLITARY*	*21*
	MULTIPLE / UNILATERAL	*15*
	DIFFUSE	*10*
WOOD (1984)	*SOLITARY*	*16.7 **
	MULTIPLE / BILATERAL	*3.1 **

Table 5.01. Retrospective series of survival in patients with colorectal liver metastases.
** = Mean survival, † = presence or absence of extrahepatic disease not stated.*

Wood (1984) reported a prospective study in 104 individuals with colorectal hepatic metastases. He found 15 (14%) had solitary metastases, 13 (13%) had metastases localized to a segment or lobe of the liver and 76 (73%) had widespread metastases. All patients with localized or widespread metastases were dead within 4 years of diagnosis while 16 % (2 patients) of those with solitary metastases were alive at 5 years. Despite the small numbers, these results confirm the favourable natural history of patients with solitary lesions. Some

caution is necessary when exalting the survival benefits of surgery in such a group as the benefits of a 25% 5 year survival following hepatic resection may not be significant when a 5 to 10% operative mortality is taken into consideration.

Clearly, when considering the influence of various treatment modalities for hepatic metastases, the result must be carefully compared to the natural history of the disease. Any comparative study should at least randomise for the extent of hepatic involvement but the influence of other factors as discussed in this section should not be underestimated.

5.2 DETECTION

The treatment of hepatic metastases, be it palliative or curative is likely to be most successful when tumour is confined to one segment or lobe of the liver in the absence of extrahepatic disease. Thus, in theory, the earliest possible detection of liver metastases is an admirable goal. Despite increasingly sophisticated techniques, it has to be admitted that in most cases treatment is performed blind to a tumour's true stage, helped in no small part by the absence of good clinical determinants of prognosis.

Liver metastases can be detected in several ways, although several techniques often have to be combined to compensate for the shortfalls of individual methods.

5.2.1 PALPATION

It is important to recognize that palpation of the liver surface at the time of surgery, often through a lower abdominal incision will miss intrahepatic deposits. In a series of 900 patients reported by Goligher (1941), there was a 11.5% incidence of synchronous hepatic metastases, but a further 16% of patients, who at surgery were felt to be tumour free and died within a short time of surgery were found to have extensive hepatic metastases at autopsy.

While the surgeon may miss metastases at laparotomy, it is also possible to mistake benign lesions for secondary deposits. In a study by Gray (1980), it was found that of 38 patients dying from gastrointestinal cancer within 1 month of surgery when the liver had been deemed to contain metastases, 3 patients were found to have benign lesions at post mortem.

5.2.2 LIVER FUNCTION TESTS (LFT)

These have the advantage of being easy and cheap to perform and are readily available in all hospitals. In early studies, Alkaline Phosphatase (AP) and Gamma glutamyl Transpeptidase (GT) were found to be elevated in over 70% of patients with liver metastases; however, the majority of patients had hepatic enlargement and the presence of metastases was suspected clinically. In a recent study in patients with known hepatic metastases, LFT failed to detect more than 50% of the metastases most of which were greater than 2 cm in diameter (Huguier & Lacaine., 1981).

Due to large hepatic functional reserves, LFT lack the sensitivity and specificity for detecting small hepatic metastases to be feasible for evaluating tumour regression following therapy or as a general screening modality.

5.2.3 CARCINO-EMBRYONIC ANTIGEN (CEA)

CEA was first demonstrated in 1965 from extracts of human colon cancer by Gold and Freedman (1965). It has been used as a marker for colorectal cancer since the early 1970's, however, the promise of identifying hepatic metastases or local recurrence at an early and therefore potentially curable stage have not been fulfilled. The main limitation is that one third of patients do not have any rise in the CEA during their disease where as others who have no evidence of disease show transient rises. This was confirmed by Moertel et al (1978) who showed a relative failure of CEA to detect local tumour recurrence, although its sensitivity was much higher for detecting liver metastases. Causes of non-specific rises in CEA include gastric and breast cancer, patients with functional hepatic impairment and inflammatory bowel disease. Despite such disappointments, recent reviews have shown that serial CEA estimations remains the best non-invasive technique for post operative surveillance following potentially curative colonic surgery (National Institute of Health Consensus., 1981). Further support came from a review by Northover (1986). The results of six large studies carried out between 1982 and 1984 were analysed. Of the 1/4 of 2147 patients (537) with colorectal cancer who had developed recurrence, 75% (404) had an elevated CEA before or at the same time as the detected recurrence.

Attempts have been made to identify specific patterns of CEA rise after potentially curative surgery. In a study by Wood and his colleagues (1980), two patterns were identified. The first was a rapid rise associated with distant metastases while a slower rise was seen predominantly in patients with local recurrence. Out of 23 patients with rapidly rising CEA (fourfold increase within 6 months) 15 patients had distant metastases with or without local recurrence. Nine out of 14 patients with a slowly rising CEA (less than 3 times normal for at least 12 months) had local recurrence alone. The outlook appeared to be worse for those patients with rapidly rising CEA. Interestingly, Hine and Dykes., (1984) were unable to show any relationship between pattern of CEA rise and the anatomical site of recurrent disease. It is therefore unrealistic to make accurate predictions on the site of recurrent disease based on patterns of CEA rise.

A controversial point is the value of second look laparotomy as prompted by a rising CEA in asymptomatic individuals and in particular, its influence on survival. A multicentre prospective trial is currently underway in the United Kingdom in an attempt to answer this question. However, some clues may be gleaned from small non-randomized studies performed. Attiyeh and Stearns (1984) performed 37 second look laparotomies in 37 asymptomatic individuals with rising CEA titres. All were considered to have had a previously curative resection for colorectal cancer. Thirty three patients (89%) were found to have recurrent disease. Liver metastases were found in 19 patients, seven of whom underwent a resection while 15 patients had locoregional disease of which 9 had a resection giving an overall operability rate of 43%. Factors influencing the resectability rate included lower CEA titres, a slower rate of rise and reduced time interval to surgery. It is not possible to evaluate the influence of such an approach on survival. Assuming that the majority of local recurrences are due to inadequate surgical excision then they may be a useful role for CEA initiated second look laparotomy although it is likely that a favourable local environment for further resection will arise in only a small proportion of patients.. In a study by Steah et al (1985), survival appeared to be better in 11 patients treated by curative or palliative resection at a CEA initiated second look laparotomy compared to a comparable group who refused reoperation. While promising, this possible survival benefit requires further evaluation.

The benefits of serial CEA estimations as early indicators of recurrent disease were bought into question by Finlay and his colleagues (1988). They demonstrated that rises in CEA occurred relatively late following the development of recurrent disease. Using growth rate studies of occult hepatic metastases, they concluded that a tumour with an average doubling time of 86 days would have a lifespan of approximately 4 years with clinical presentation occurring 2 years from initial implantation. In a follow up study of 8 patients with occult hepatic metastases detected by CT at the time of an apparently curative resection, the rise in CEA became evident 7.5 months following radiological diagnosis. The median interval from initial CEA rise to death was 5.5 months. Despite some reservations concerning the application of mathematical models to biological problems, this work highlights the extraordinary length of the disease process. It would seem that rises in CEA titres lag to a stage when cure of recurrent disease in most instances is beyond the reach of conventional treatment.

In conclusion, there is still a need for a simple and sensitive biochemical assay to detect biologically early recurrent disease. This begs the question that if such an assay was to be developed, is there an imaging technique sufficiently sensitive to locate the site of recurrent disease.

5.2.4 IMAGING

Biochemical indices have several obvious disadvantages. They fail to provide information on the number, size and site of metastases and their relationship to biliary and vascular structures. Clearly some form of imaging is necessary to provide such information to select patients who may benefit from excision of recurrent disease at the earliest possible stage when the prospect of cure is highest.

The ideal imaging modality should be fulfil certain criteria :-

1) It should be widely available.

2) Simple to perform preferably without ionising radiation.

3) Suffer no operator error i.e results are easily reproducible.

4) Require no allergenic or toxic substrates.

5) Have a high sensitivity and specificity.

It comes as no surprise that no one technique can satisfy all these requirements. Sensitivity (ratio of those tested positive compared to all those with the condition) and specificity (ratio of those tested negative compared to all those without the condition) ratios are quoted as barometers of the efficacy of various imaging techniques. Comparison of figures from different series must be interpreted with some caution since they depend upon the denominator in the equation; that is all those with or without the condition under test. This can be determined in several ways :

1) Surgical exploration with biopsy - This is likely to miss lesions within the liver substance and assumes all abnormalities are malignant. For this reason biopsy is essential although is liable to sample errors.

2) Follow up - If the follow up time is too short, then it is likely that the number of metastases will be underestimated.

3) Pathological assessment of surgical specimen. This is the most accurate and should be regarded as the gold standard. It of course assumes that portion of the liver not removed is tumour free.

This section will consider the limitations of currently available imaging techniques.

5.2.4.1 RADIONUCLIDE IMAGING

This technique has been the mainstay of liver tumour detection for many decades. It is easy to perform and relatively inexpensive. The smallest diameter lesions detectable is in the order of 1.5 to 2.0 cm using the most recent technical advances. Despite the inherent difficulties in confirming the presence or absence of liver involvement as previously discussed, sensitivities of 70 to 80% are quoted for detecting liver lesions. However, the main problem is that all space occupying lesions within the liver appear the same on radionuclide imaging. The low specificity (Lima et al., 1975, Ostfeld & Meyer., 1981) inevitably requires a second investigation to determine the nature of the lesion.

Compared to CT and US, the lack of spatial resolution in particular to major vascular and biliary structures coupled with poor tissue characterization are major drawbacks. These factors limit the adoption of liver scintigraphy as a primary diagnostic tool in the detection of liver cancer.

5.2.4.2 HEPATIC FLOW SCINTIGRAPHY

This technique has been described as a method of enhancing sensitivity and specificity of hepatic imaging. Unlike the normal liver which receives 20% of its total blood supply from the hepatic artery, metastases derive almost their entire blood supply from this source. This inturn produces an altered flow pattern with the liver receiving an increased proportion of arterial blood. This can be quantified using a scintigraphic analysis expressing the ratio of arterial blood flow to total hepatic blood flow.

In a prospective study, 151 patients were studied with the absolute determinant of liver metastases being palpation and follow up (Levenson et al., 1985). A reported sensitivity of 96% and a specificity of 72% were reported. However, lesions under 2 cm in diameter cannot be imaged by radionuclide techniques and therefore this technique is unlikely to have a large role in screening. Its second drawback is the lack of information regarding relations of metastases to major vascular structures.

5.2.4.3 ULTRASOUND (US)

This technique has many factors in its favour. It is widely available, non-invasive, simple to perform with rapid examining speeds. Its main weakness is that its efficacy is highly operator dependant with enthusiasts reporting excellent results. It is generally accepted that focal hepatic lesions less than 2 cm in diameter cannot be reliably detected by US. The most optimistic study using linear array transducers report detection of lesions as small as 11 mm (Sheu et al., 1985). There is no strong correlation between sonographic appearance and histological type (Green et al., 1977), therefore, tissue specificity is poor making fine needle aspiration and core biopsy of suspected metastases a necessity for confirmation. When combined, such an approach can achieve sensitivity and specificity rates of 92% and 100% respectively making it as accurate as laparoscopic guided liver biopsy but much less invasive (Montali et al., 1982). In a prospective study comparing US, CT and scintigraphy to detect biopsy proven metastatic cancer, there was no significant differences in sensitivity and specificity between these three imaging modality (smith et al., 1982).

A recent useful extension of US is its intra-operative application for the detection of small (diameter < 2cm) intrahepatic focal lesions. The absence of a soft tissue interface between the transducer and the liver allows higher frequencies (5 to 12.5 MHz) to be used enhancing spatial resolution. This approach is not in wide use but it is gaining increasing recognition. Thomas et al (1987) undertook an in-vivo study in 20 post mortem livers removed from patients who died from gastric or colorectal cancer and determined the correlation between direct contact US and histological examination of serial slices of liver for detecting liver metastases. Of 67 lesions, 45 were successfully imaged (67%), 35 out of 37 lesions greater than 1 cm (95%) were detected, while 10 out of 15 metastases 0.5 to 1.0 cm were imaged. None of the 15 metastases less than 0.4 cm in diameter were picked up. The authors had no previous experience yet there were no false positives.

An evaluation of intra-operative ultrasound (IOUS) was carried out by Machi and his colleagues (1987) in 84 patients undergoing surgery for colorectal cancer. All patients had preoperative US and CT scans of the liver. Of 46 metastases detected, 32 were imaged by preoperative investigation and or palpation of the liver. Of these, 31 were detected by IOUS in addition to a further 14 giving an overall detection rate of 98% (45/46) with an increased detection rate of 28% over preoperative assessment. All metastases were less than 2 cm in diameter and located deep within the liver substance. In a similar study, Kane and his colleagues (1987) found a 25% increased detection rate, the higher sensitivity rate favouring small lesions. In none of these studies is a false positive rate quoted. Several other workers have confirmed the increased sensitivity of IOUS and in addition, assessed the impact of this technique on surgical decision making (Gozzetti et al., 1986, Machi et al., 1986, Rifkin et al., 1987, Bismuth et al., 1987). All reported that IOUS provided additional information in up to 30% of all patients resulting in a change of management or surgical approach.

IOUS reliably detects metastases down to 0.5 cm in diameter deep within the liver substance with its associated implications on management. What influence this has on patient survival is not clearly known and is likely to be difficult to assess in a randomised controlled trial as a non-IOUS arm maybe unacceptable on ethical grounds. However, its ability to delineate the relationship between tumours and intrahepatic biliary and vascular

structures will ensure it has an important role in the planning of hepatic resections. The routine adoption of IOUS at the time of primary tumour resection would be an ideal goal for accurate tumour staging. However, it may be impractical in those instances where exposure of the liver involves extending the incision with prolongation of operating time.

5.2.4.4 COMPUTERISED TOMOGRAPHY (CT)

This is the commonest method employed for detecting hepatic lesion and depends on differences in the x-ray attenuation pattern between metastases and normal liver parenchyma. This, in practice, is very little and various water soluble contrast agents are employed to enhance the attenuation of the normal parenchyma or the metastasis.

In a review, Clark and Matsui (1983) defined 7 methods of CT scanning with water soluble contrast agents. The contrast may be administered intravenously in one of two ways. The first is by intravenous infusion or alternatively by rapid bolus administration with immediate dynamic sequential scanning as the contrast is injected. It is possible to combine both these methods which rely on higher uptake of contrast by the normal parenchyma than the tumour. The bolus technique however achieves a better differential as there is less time for the contrast to diffuse into the tumour. However, this method requires third or fourth generation scanners capable of rapid scan times with short interscan delays. A disadvantage of this approach is that large doses of contrast may need to be given leading to nausea and vomiting in many patients.

An alternative approach is to administer the contrast intra-arterially (CT arteriography). Hepatic metastases derive their entire blood supply from the hepatic artery unlike the normal liver which only derives 20% of its total supply from this source. Injection of contrast into the hepatic artery exploits this fact leading to increased opacification of the metastases. CT arterial portography relies on injection of the contrast into the superior mesenteric artery producing selective opacification of the portal venous blood. Unlike metastases, the normal parenchyma shows increased opacification. CT arteriography and portography are invasive and costly. In addition, the necessity for hospital admission and morbidity of an angiogram make both these techniques unsuitable for routine use.

Delayed scanning provides another way of delineating between normal parenchyma and metastases. Three to six hours following contrast administration, there is increased opacification of normal liver due to contrast in the hepatocytes and biliary systems. Metastases, unable retain the contrast for this length of time appear as filling defects. The disadvantages of this approach include large contrast doses, doubling of the radiation doses and examination times with their implication on cost.

EOE-13 is a 53% aqueous emulsion of iodinated poppy seed oil developed by Vermes and his colleagues at the National Institute of Health (1979). This material in taken up selectively by reticulo-endothelial cells in the liver and spleen but not by metastases within them thereby allowing selective opacification of normal parenchyma. However, EOE-13 is relatively unstable with limited availability and in up to 60% of patients produces chills and fever (Miller et al, 1984). It is regarded by many as an experimental agent only.

There is now a wealth of evidence recognizing that contrast enhancement is essential for reliable detection of liver metastases, however, much controversy surrounds the optimal method of delivery and the timing of the scans. In a prospective study by Pausher et al (1989), hepatic CT scans were performed in 50 patients using no contrast compared to rapid contrast infusion and bolus contrast administration with rapid sequential scanning. The latter technique detected 10% and 15% more lesions than the infusion approach and non-contrast imaging respectively. Other workers have also shown the superiority of bolus administration detecting as many as 40% more lesions than non-contrast and infusion approaches (Berland et al., 1982, Burgener & Hamlin., 1983). Using bolus administration, Freeney et al (1986) showed a 73% sensitivity and a 99% specificity in detecting liver metastases from colorectal cancer confirmed by histology at laparotomy. Bernardino and his colleagues (1986) attempted to assess the value of delayed scans combined with bolus administration and dynamic sequential scanning in the same patient. Both these techniques identified the same number of patients, the delayed scan providing better definition of metastasis architecture while detecting more lesions in 27% of patients. However, some 11% of lesions were better visualised on the dynamic images. There were no false positives with either technique and on balance the two techniques would seem complimentary.

Other investigators have attempted to improve the accuracy of CT by injecting contrast material into the superior mesenteric artery (CT portography) or the hepatic artery (CT arteriography). Matsui and his colleagues (1987) compared the sensitivity of conventional ultrasound, dynamic sequential CT after bolus administration, CT arteriography, CT portography and CT after intra-arterial injection of iodinated poppy seed oil in detecting 45 colorectal hepatic metastases resected in 22 patients. The respective sensitivities were 58%, 63%, 50%, 84% and 38%. Of 18 lesions less than 15 mm in diameter, 10 were detected by CT portography alone. Five out of 7 lesions not visualised by CT portography were less 5 mm in diameter, however, this technique was falsely positive in 4 out of the 22 patients. The low relative specificity of CT portography has also been reported by other workers (Miller et al., 1987) making ultrasound or conventional CT essential to exclude benign lesions such as cavernous haemangioma, cysts, adenomas, fibronodular hyperplasia and abscesses. While invasive and specialized, CT portography is useful in delineating the relationship of metastases to major vascular structures. The low detection rate reported by Matsui and his colleagues for EOE-13 has not been confirmed by other workers. For example, Miller et al (1984, 1987) in a comparison of EOE-13 enhanced scans and surgical histological findings noted a 77% detection rate which was twice as many as either unenhanced or water soluble contrast enhanced CT.

The difficulty of comparing sensitivity and specificity of imaging techniques in different series has been previously discussed. With CT imaging, this problem is further compounded by non-uniform methods (contrast volume and administration rate, timing and types of CT scanners) practiced for any given enhancement technique. Thus only broad generalisations can be made regarding the optimal CT enhancement method.

As discussed in the next chapter, CT scanning formed the principle imaging modality in detecting and assessing the response of liver metastases following interstitial laser therapy. Tumour detection at the earliest possible stage is likely to determine the results of ILH and subsequent benefit to patients. It is therefore important that the optimum contrast technique for CT imaging of metastases is employed. On the basis of the literature review presented in this section, the combined bolus and infusion technique with delayed

scans probably represents the optimum and most practical method of CT imaging of focal hepatic lesions.

All images presented in chapter 6 were obtained using a Siemens CT scanner (Somatom, DR). Detection of metastases was performed using contiguous 8 mm slices. Oral and intravenous contrast were given. The latter as a bolus and an infusion during scanning. Oral contrast was administered 20 minutes and immediately before initial liver scanning. Scans through the same area were repeated immediately following 100 ml bolus of intravenous contrast plus 50 ml during scanning. Delayed scans through the same area were repeated 45 to 60 minutes after injection. Post laser imaging consisted of liver scanning immediately following bolus injection of 100ml of intravenous contrast with 50 ml administered during scanning.

5.2.4.5 MAGNETIC RESONANCE IMAGING (MRI)

MRI is an effective method for detecting hepatic metastases which does not require ionizing radiation or injection of toxic or allergenic substances. It is not the place of this review to discuss the detailed mechanics of this imaging modality but as with CT scanning, results vary with technique and instrumentation.

The real question posed by MRI is whether it has any useful advantages compared to CT scanning ? In a prospective multi-institutional study, Chezmar et al (1988) compared the detection rate of hepatic metastases in 59 patients using CT (Dynamic sequential + delayed scans) versus MRI. The absolute determinant for the presence of hepatic metastases were surgical exploration, biopsy and follow up. Of 28 patients with malignant liver disease, MRI demonstrated this in 27 (96% sensitivity) and CT in 26 (93% sensitivity). However, the false positive rate for MRI was 26% (8/31) compared to 6% (2/31) for CT. Of 16 patients with significant extrahepatic findings, CT detected this in 12 and MRI only in 1. This difference is statistically significant and is confirmed in similar studies by Glazer et al (1986) and Stark et al (1987).

However, differences between CT and MRI seem not to be clear cut. Several studies have focused on comparing the efficacy of CT and MRI for detecting focal hepatic lesions. Some have found CT superior (Glazer et al., 1986, Nelson et al., 1988) while

others have found the converse to be the case (Reinig et al., 1987, Stark et al., 1987). These differences probably reflects various CT and MR techniques used with different equipment and design studies. The drawbacks of MRI are limited availability, prolonged examination times and limited depiction of extrahepatic structures. For the moment, the real differences between CT and MRI are probably small. The availability, experience and superior extrahepatic delineation would favour CT especially when used in dynamic sequential mode after bolus administration (an accurate indicator of patients with hepatic disease) with delayed imaging (an accurate indicator of the number of lesions).

MRI performance may be improved with the use of contrast media. A supraparamagnetic iron oxide agent which is taken up selectively by normal liver tissue has been tried with worthwhile improvements (Stark et al., 1988). For the moment this agent must be regarded as experimental.

5.3 TREATMENT

The value of any treatment is judged by its influence on the natural history of the disease process. It may prolong life and or improve its quality. The trade off for the patient for such gains must be an acceptable low risk of serious complications. Given the retrospective nature of most studies, the ethical implications of withholding any treatment however experimental for a condition which is uniformly fatal, it is debatable whether the natural history of liver cancer is fully understood. Therein lies the conundrum. How to assess the curative or palliative value of any treatment when formidable ethical and moral obstacles prevent a scientific approach to understanding the natural history of a common problem. However, as clinicians we have to make a choice between therapeutic nihilism and unjustified aggressiveness involving substantial risk to the patient.

5.3.1 HEPATIC RESECTION

The first hepatic resection for colorectal metastases was performed over 100 years ago in Germany (Garre., 1888). In the last 10 years, there has been a large increase in the number of minor and major hepatic resections carried out due in part to a greater

understanding of the segmental anatomy of the liver, improved surgical and anaesthetic techniques and a more aggressive approach to the management of hepatic tumours.

Hepatic resection is the only treatment which offers the prospect of cure. However, it is only appropriate for a small group of patients variously estimated at 5 to 10% of those with colorectal metastases and 9 to 17% with hepatocellular carcinoma (Fortner et al., 1984, Okuda., 1980, Lee et al., 1982). Much controversy surrounds the true value of hepatic resection. In this section I shall put forward both sides of the argument. Due to their high frequency, colorectal hepatic metastases as a group have been best studied and provide the hard core of available data. In addition, their biological behaviour is more favourable than upper gastrointestinal cancers and it is relatively easy to achieve locoregional control of the primary tumour while the pattern of haematogenous spread is relatively well defined.

I) AGAINST HEPATIC RESECTION:

1. The natural history of hepatic metastases against which the value of surgical resection must be judged has only been studied using retrospective historical controls. This is fraught with bias and misinterpretation.

2. The phenomenon of lead time bias needs to be taken into account. In most instances historical controls against which the influence of hepatic surgery is measured date before the 1970's when the diagnosis of hepatic metastases was made clinically and therefore late in the natural history of the disease. Modern CT and US imaging detect metastases much earlier and thus it is debatable whether prolongation in survival is really due to surgery or merely earlier diagnosis. A lead time bonus of 3.7 years has been suggested on the basis of cell kinetic studies (Finlay et al., 1988) giving a reported 2 year survival of 20% as the true 5 year survival rate for untreated solitary lesions. This does not differ significantly from 5 year survival rates following surgery.

3. A prospective study by wood (1984) in 104 patients revealed a 5 year survival rate of 16% in those with solitary lesions. It is therefore debatable whether any survival benefit conferred by hepatic resection is really due to removal of the metastases or merely the result of a highly favourable natural history in a highly selected group.

4. The most sensitive pre-operative and intra-operative investigations are unable to determine the true extent of spread making rationale selection of suitable patients for treatment impossible. Thus a significant number of patients are exposed to an unnecessary procedure with its associated risks to survival and quality of life without any discernible benefit.

5. In series of major hepatic resection for colorectal metastases published in the last decade, the operative mortality has ranged from 4 to 12% (Fortner., 1984, Adson et al., 1984, August et al., 1985, Butler et al., 1986) and in those series where complications were reported, up to 25% of patients suffered a serious untoward effect (August et al., 1985, Logan et al., 1982). Mortality figures are often not included in many authors survival figures which if taken into account, may negate any advantage of hepatic resection.

6. Doubling time studies have estimated the mean age of occult metastases (not evident to the surgeon at operation but detected by CT scan in the immediate post operative period) is 2.3 $\pm$ 0.4 years while overt metastases (detected by surgeon at operation) dated 3.7 $\pm$ 0.9 from implantation (Finlay et al., 1988). The staggering time scales involved make it very unlikely that the concept of truly solitary metastases exist.

7. Any palliative value derived from hepatic resection may be achieved by non-surgical means at much lower risk to the patient.

II) FOR HEPATIC RESECTION

1. Hepatic resection offers the only hope of cure for a small number of patients and no matter how slim that possibility, it should not be denied. Optimistic figures suggest 20 out of every 100 patients with colorectal hepatic metastases is suitable for hepatic resection. Of these, 6 to 8 will survive 5 years or more following surgery. However, 1 to 2 of these 5 year survivors will still succumb to recurrent disease leaving 5 to 7 patients of the initial 20 operated on emerging as cures. It is estimated that there are 600 patients each year in the United Kingdom with colorectal hepatic metastases suitable for resection. If all were offered surgery , then this would translate to 150 to 210 individuals cured.

2. Hepatic resection may have a palliative value by prolonging survival even in those developing recurrent disease. Admittedly, this benefit is difficult to quantify but should not be underestimated.

3. Despite the misgivings of historical controls, hepatic resection offers a clear survival advantage.

4. Improvement in survival following hepatic resection outweighs the operative mortality of surgery which in the latest series is less than 5% (Scheele et al., 1990).

5. The time bonus associated with lead time bias could be attributed to patients undergoing surgery as well because they do not differ significantly in respect of tumour size and extent from matched historical controls.

6. Statistical analysis when applied to complex biological phenomena are only of value when these phenomena can be fully identified and numbered.

The arguments presented illustrate the immense difficulty in interpreting this area of the literature. The same report can be interpreted to either support or refute the concept that surgery is beneficial. For the moment, the demonstrable benefits of surgery are probably not sufficiently large to offer complete support to proponents of this approach. However, when a purely scientific approach to selecting patients is not possible then experience and personal philosophy of the individual surgeon must be bought to bear. Selection can then be based on those whose chance of long term survival is greater than any potential risk from hepatic resection. For example, those individuals with 4 or less colorectal metastases in a unilobular distribution with no extrahepatic disease. It must be possible to excise all macroscopic disease with an uninvolved margin of at least 1 cm. Accepting that in excess of 75% of patients operated on will not be cured, then any palliative value can only be justified if an intended resection has an operative mortality of 5% or less.

The difficulty for the surgeon faced with a fit patient with localised operable hepatic metastases is elegantly summed up by Adson from the Mayo Clinic (Adson et al., 1987) 'We cannot always act so that hope might triumph over judgment, but we must not ignore the patient's need for hope when operative risk and morbidity is low, when there are no therapeutic alternatives, and when, at times, palliative efforts may give rise to cure. We

should hope to blend our science and our humanity into an art that our patients can perceive as grace.'

5.3.2 CHEMOTHERAPY

Over the pat 30 years, chemotherapy has been the leading palliative treatment for those unsuitable for hepatic resection. Is this position justified ? It has to be said that interpreting the literature in this area is difficult for several reasons. Invariably there is poor documentation of the spread of disease, in particular, primary tumour site/histology, extent of hepatic involvement and the presence or absence of extrahepatic disease. The issue is further complicated by use of numerous agents in various combination at various doses using different administration schedules and varying routes. There are two principle means of drug delivery. These are systemic (intravenous route) and regional intra-arterial (hepatic artery) administration.

Most patients with hepatic metastases invariably have overt or occult systemic disease. For this reason systemic administration is a biologically attractive concept, however, normal tissues maybe unnecessarily exposed to potent cytotoxic agents with its attendant problems. An unacceptable incidence of serious systemic problems including bone marrow depression, severe diarrhoea and mucositis have greatly increased the patient's morbidity. Invariably, this approach has yielded poor results in terms of survival with a response rate less than 20% (Moertel., 1975). In conclusion, there is very little evidence to support either single agent or combination systemic chemotherapy for colorectal hepatic metastases.

Severe side effects and difficulties in long-term maintenance treatment have stimulated a search for alternative administration routes of which the regional route is most widely used. The concept of delivering cytotoxic agents directly into the tumour's arterial blood supply is based on anatomical and pharmacological principles. Unlike the normal liver parenchyma which derives 80% of its blood supply from the portal circulation and 20% from the hepatic artery, metastases gain their blood supply almost exclusively from the hepatic artery (Taylor et al., 1979). Hepatic artery infusion has the theoretical advantage of exposing the tumour to high local concentrations of the drug with much reduced

systemic levels. The incidence of toxic effects is thus lowered. This assumes that the cytotoxic agent has a high 'first past' effect, that is the vast majority of the drug is extracted as it flows through the liver with little spill over into the systemic circulation. The hepatic artery can be cannulated either surgically or percutaneously using a seldinger technique. In the event of anomalous blood supply then 2 catheters may be necessary which were initially connected to external pumping devices. Poor patient compliance and technical difficulties limited the usefulness this approach, however, the advent of a totally implantable delivery system has overcome these problems (Blachshear., 1979). This consists of a small lightweight, silent device with a chamber placed in a subcutaneous pouch.

In contrast to the percutaneous approach, sepsis, hepatic artery thrombosis, catheter misplacement are rarely seen following surgical placement. The commonest agents used are 5-Fluorouracil (5-FU) and 5-Fluoro-2-deoxyuridine (FUDR). A number of non-randomised studies have been conducted using these drugs, however, the caveats previously discussed regarding data interpretation make the results of little use. However, in a recent randomized study, regional intra-arterial FUDR was compared with systemic venous administration (Chang et al., 1987). Objective signs of response were seen in 62% of the first group and 17% of the second group. There was no significant difference in actuarial survival rates at 24 months (22% and 15 % respectively). Long term intra-arterial administration was associated with significant problems including chemical hepatitis (79%), biliary sclerosis (21%), peptic ulceration (17%) and gastritis/duodenitis (21%). Invariably it was the responders who developed these problems limiting the value of long term administration. In addition, two new problems have emerged (Balch and Levin., 1987, Bengmark., 1989). Treatment directed at one region, for example the liver, results in compensatory growth outside that region (lung, bone, brain). Secondly, after each treatment cycle to the liver, there is often rapid compensatory growth making the end result seem as if no treatment has been carried out. Of practical importance is the high cost of infusion pump devices (£2500) plus expenses of hospitalisation and surgery which would make wide scale adoption of this approach impractical.

An alternative approach to the problem of hepatic metastases is adjuvant chemotherapy at the time of colorectal cancer excision in an attempt to destroy liver

micrometastases and circulating malignant cells likely to implant. Several trials have now shown that adjuvant systemic chemotherapy has no significant effect on survival following resection for colorectal cancer (Douglass., 1987). Given that tumour cells are likely to be present in the portal circulation at the time of surgical resection, it would seem logical to use this route for adjuvant drug administration to reduce the subsequent incidence of hepatic metastases. Taylor et al (1985) treated 117 patients compared to a control of 127 by immediate post operative infusion of 5-FU via the portal vein. Over a 4 year follow up, only those with Dukes B cancers in the treatment group derived a significant improvement in survival.

In conclusion, while increasingly innovative approaches to maximise cytotoxic drug delivery to tumours are devised, the limiting factor in the equation remains the limited efficacy of cytotoxic drugs. Until more effective agents are developed, it is unlikely that any improvements in the results of chemotherapy will be seen. For the moment, continuous hepatic artery infusion should not be used outside the setting of controlled clinical trials.

5.3.3 ISCHAEMIA

Hepatic metastases derive their entire blood supply from the hepatic artery while normal hepatic parenchyma has a dual supply from hepatic artery and portal vein. This has provided the rationale for attempts at tumour growth retardation by hepatic artery ligation, total hepatic dearterilization and intermittent hepatic artery occlusion.

Simple hepatic artery ligation does not significantly prolong survival compared to the natural history of colorectal hepatic metastases (Almersjo et al., 1972, Bengmark et al., 1974). In some situations, good results have been obtained, for example, pain relief due to extensive tumour volume and patients with carcinoid tumours where relief of symptoms is associated with a fall in the 5-hydroxy-indole acetic acid excretion.

The development of collateral arterial circulation following hepatic artery ligation was combated by extensive surgical procedures to prevent this occurring. However, most results are anecdotal and even then, most workers regard dearterialization alone as insufficient to control tumour growth in the liver. The connections between the hepatic artery and the portal vein that open up following hepatic artery occlusion in some way

account for the disappointing results of this form of treatment. It can therefore only be recommended in very selected cases.

5.3.4 HEPATIC ARTERIAL EMBOLISATION

This represents another way of exploiting the arterial tumour circulation. The technique is performed under local anaesthesia by passing a cannula into the femoral artery up the coeliac axis where the hepatic artery and its branches can be selectively occluded using a variety of materials such as starch, albumin microspheres, sterile gelatin sponge, lyophilised human dura mater and steel coils. A drawback to this approach is that it cannot be performed on an ambulatory basis.

Most reports on the value of embolisation are anecdotal or are derived from uncontrolled studies. However, limited success has been reported in patients with hepatocellular carcinoma and endocrine tumours such as carcinoid and islet cell tumours with immediate and sustained improvements (Maton et al., 1983). Unfortunately, colorectal metastases generally prove resistant to this method of treatment although there is evidence to suggest symptomatic benefit in those patients with pain due to capsular distension (Taylor., 1985). It is worth emphasizing the significant morbidity associated with this technique. Nausea, vomiting, fever, abdominal pain, paralytic ileus and transient derangements of the liver function test are seen in almost all patients. In addition, severe untoward effects such as gall bladder infarction, delayed gall stone formation, acute pancreatitis, hyperuricaemia, gastroduodenal bleeding and hepatoma rupture have been reported (Jeng and Ching., 1988). Three deaths related to embolisation have been reported in one series (Wallace et al., 1984).

5.3.5 RADIOTHERAPY

The efficacy of external beam radiotherapy is limited by the presence of a radioresistant tumour in a relatively radiosensitive organ. The maximum dose that can be tolerated by normal hepatocytes is in the order of 30 to 40 Gray which is too low to be curative. Doses in excess of 30 Gray result in a high incidence of radiation hepatitis

(Thomas., 1984). Where external beam radiotherapy has been of value is in palliation of abdominal pain due to large tumour volumes (Borgelt et al., 1981).

In an attempt to overcome the problems of radiation hepatitis, a number of studies have explored the use of internal radiotherapy, for example, by injecting yttrium-90 microspheres (Byfield et al., 1984). Objective tumour regression and improvement in patients' symptoms have been reported but there is no good evidence that survival is improved (Grady., 1979, Ariel & Padula., 1978).

The value of radiotherapy lies in palliation of severe pain due to capsular distension by large tumour bulk. There is no good evidence that survival is enhanced at safe therapeutic doses.

5.4 CONCLUSIONS

Hepatic resection offers the only chance of cure but is only appropriate in a small number of patients with metastatic liver disease. Much controversy surrounds the true value of such aggressive treatment for what is regarded by many as a manifestation of widely disseminated disease.

In a review on treatment of colorectal hepatic metastases, Taylor (1985) concluded "Hepatic artery ligation, hepatic dearterialization, liver irradiation and systemic chemotherapy have not been shown to produce worthwhile benefit either in terms of palliation or survival." Malik and Wrigley (1988) on assessment of the value of intra-arterial hepatic chemotherapy were unconvinced of any survival benefits. The inadequacies of palliative treatment of hepatic tumours were recently highlighted by Bengmark (1989) in a leading article in the British Journal of Surgery. His last thoughts on the matter were "..... attempts should be made to develop a palliative treatment for patients with liver tumours which is simple, can be performed on an ambulatory basis for life, involves active participation by the patient, and which has minimal or no side-effects. Such treatment should not reduce mental and physical activity. At present the goal should be growth control and not cure."

It was in pursuit of these goals that the work in the next section was carried out.

CHAPTER 6. INTERSTITIAL LASER HYPERTHERMIA FOR LIVER METASTASES.

6.1 INTRODUCTION

The epidemiology, natural history and limitations of current treatment for hepatic metastases have been discussed in the previous chapter. In a review of palliative treatment for hepatic tumours, Bengmark (1989) came to the conclusion that there is a need for a simple safe technique whose principle aim would be palliation by controlling local tumour growth. As survival is dependant on the extent of hepatic involvement, then arresting or reducing tumour volume may lead to improved patient survival. Alternatively, life quality may be enhanced by delaying the onset of symptoms arising from compression of vital structures such as the inferior vena cava.

Interstitial therapy, a relatively new concept in oncology goes some way to fulfilling Bengmark's criteria. The term interstitial pertains to the delivery of a therapeutic modality, for example, heat directly to a selected site where tissue necrosis is required. In the context of cancer therapy, selective tumour necrosis can be achieved with sparing of surrounding normal tissue. The focal nature of tissue damage makes interstitial therapy unsuitable for treating diffuse or multiple liver tumours. Interstitial techniques can be divided according to the type of agent producing cell death.

1) Heat - for example, laser, radiofrequency and microwaves.

2) Cold - achieved using liquid nitrogen.

3) Chemical means - such as alcohol and phenol.

4) Ionising radiation - using radioactive x-ray implants.

The concept and experimental data on interstitial laser hyperthermia (ILH) have been described in chapter 3. The success and safety of ILH in treating liver metastases depends on several interrelated factors.

1) Accurate identification with precise mapping of tumour extent.

2) Accurate laser fibre placement (preferably percutaneously) within the tumour.

3) Identification of real time tissue changes and their significance to the extent of tumour necrosis.

4) Visualisation of the extent of tumour necrosis following treatment with subsequent healing.

5) Delineating residual or recurrent viable tumour for further treatment.

The first clinical work using ILH for liver tumours was reported by Hashimoto and his colleagues in 1985. A similar study was performed by Schroder et al (1989) using this technique in 4 patients with hepatic metastases. In both series, a laparotomy was necessary for laser fibre insertion into the tumours. This makes the technique relatively invasive and excludes those unfit for surgery. In addition, hospitalisation and recovery times are relatively long. Given the palliative nature of ILH, an operative approach for fibre insertion is undesirable.

Experimental work has confirmed the feasibility of relatively precise percutaneous fibre placement in animal liver using ultrasound guidance (Bosman et al., 1991, Dachman et al., 1990). The work presented in this chapter is a clinical pilot study using a percutaneous approach with ultrasound guidance for fibre insertion to treat hepatic metastases. There were two principle objectives. The first was to assess the feasibility of such an approach for inducing necrosis in liver cancer and secondly to evaluate whether this could be achieved safely. This study had the approval of the local ethical committee.

By way of contrast, alternative interstitial techniques used in treating liver cancer are reviewed to assess the relative strength and weakness of each thus providing a basis for what is likely to be the optimum technique. In the absence of controlled clinical trials, such an assessment must be treated with some caution.

6.2 METHOD

Between November 1988 and August 1991, 21 patients with hepatic metastases were referred to the National Medical Laser Centre to be considered for ILH. Treatment selection was relatively flexible and included the following criteria. A positive histological diagnosis of liver cancer was made whenever possible with no remaining evidence of the primary tumour or extrahepatic spread. No patient was to have more than 4 hepatic deposits with none exceeding a diameter of 6 cm. All lesions must be accessible to percutaneous

puncture. Patients were to be unsuitable for hepatic resection on grounds of unfitness, tumour inoperability or to have refused surgery.

Detection of synchronous hepatic metastases during resection of the primary, rising tumour markers or surveillance sonography showing features consistent with hepatic metastases were the commonest reasons for referral. Eight patient were turned down due to multiple metastases, extrahepatic spread or excessively large tumours where the probability of worthwhile tumour regression was considered to be small. Twelve patients (mean age 64 years, range 53-77 years) with a total of 33 hepatic metastases (mean diameter 3.5 cm, range 1.0-11.0 cm) received a total of 52 laser treatments (range 1-8 per patient) using a percutaneous technique. Patient details are summarised in table 5.01. The primary tumour site was the colon in 6 patients, the rectum in 3 with the oesophagus, stomach and a small bowl carcinoid each accounting for the remaining 3 patients. Five patients had synchronous hepatic metastases at the time of resection of the primary lesion with the remainder developing metachronous metastases. The mean interval from primary resection to first laser treatment was 30 months (range 5-108 months). Mean follow up time was 20 months (range 4-40 months). Informed consent was obtained from all patients.

NUMBER OF PATIENTS	*AGE (YEARS)*	*PRIMARY CANCER SITE*	*NO. OF HEPATIC TUMOURS*	*METASTASIS DIAMETER (CM)*	*TOTAL TREATMENT NUMBER*
7 Male 5 Female	53 - 77 Mean = 64	75% Colorectum	33	1.0 - 11.0 Mean = 3.5	52

TABLE 6.01. Patient Demographic Data

All patients were questioned and examined carefully prior to treatment to exclude any overt extrahepatic disease. Those with a previous history of a colonic or rectal resection with rising carcino-embryonic titres had been screened colonoscopically by the referring physician to exclude recurrent or a metachronous bowel carcinoma. In addition, a pelvic CT scan was included in the work up of rectal cancer patients. Baseline liver function tests, full blood count, clotting screen and urea and electrolytes were performed. Serum was

grouped and saved and a chest radiograph performed to exclude pulmonary metastases. Tumour markers were assayed where appropriate.

Pre-treatment hepatic imaging consisted of ultrasound (Aloka 650, Japan) using a 3.5 or 5.0 MHz transducer and a dynamic contrast enhanced computerised tomographic (CT) scan (Siemens, Somatom, DR) with pre-contrast and delayed images. The protocol for CT imaging was as follows. All scans were taken using contiguous 8 mm sections through the liver. Oral contrast was given 20 minutes and immediately before scanning. Dynamic scanning was then repeated through the same area immediately following a 100ml bolus of intravenous non-ionic contrast (Iohexol, 350mg/ml)) with a further 50ml during rapid scanning through the liver. Total scan times were of the order of 6 minutes. Finally, a delayed scan through the same area were performed 45 to 60 minutes after injection. On the basis of this, the enhancement pattern, number, site and size of the metastases were determined.

All Treatments was performed using a continuous wave Nd:YAG laser (Flexilase, Living Technology, Glasgow) coupled to a 1x4 200 micron star coupler (Canstar, North York, Ontario, Canada). This allowed the simultaneous transmission of laser light of equal intensity down 4 fibres from a single output source from one laser. The fibres were prepared for each treatment in the following way. The distal end of each fibre was cleaved perpendicular to its long axis. The protective plastic cladding was stripped off the terminal 1.5 cm of each fibre exposing the bare silicon core. The quality of the cleave was checked using the Helium-Neon aiming beam on a white background. A good cleave produced a sharp well defined spot of red light. Conversely, a suboptimal cleave produced a ragged poorly focused spot. The implications of the latter is inhomogeneous tumour heating due to poor collimation of the emitted laser light. The fibres were then calibrated using a power meter (Coherent, Oxford, U.K) by adjusting the laser output to produce a stable power of 1.5 to 2.0 watts per fibre. The fibres were then immersed in a glutaraldehyde bath for 10 minutes, rinsed in sterile saline and then dried.

All treatments were performed in an endoscopy suite using a combination of intravenous sedation and analgesia (Diazepam 5-10mg & Pethidine 50-75mg) together with a 24 hour regimen of intravenous prophylactic antibiotics (Flucloxacillin 500mg 6 hourly &

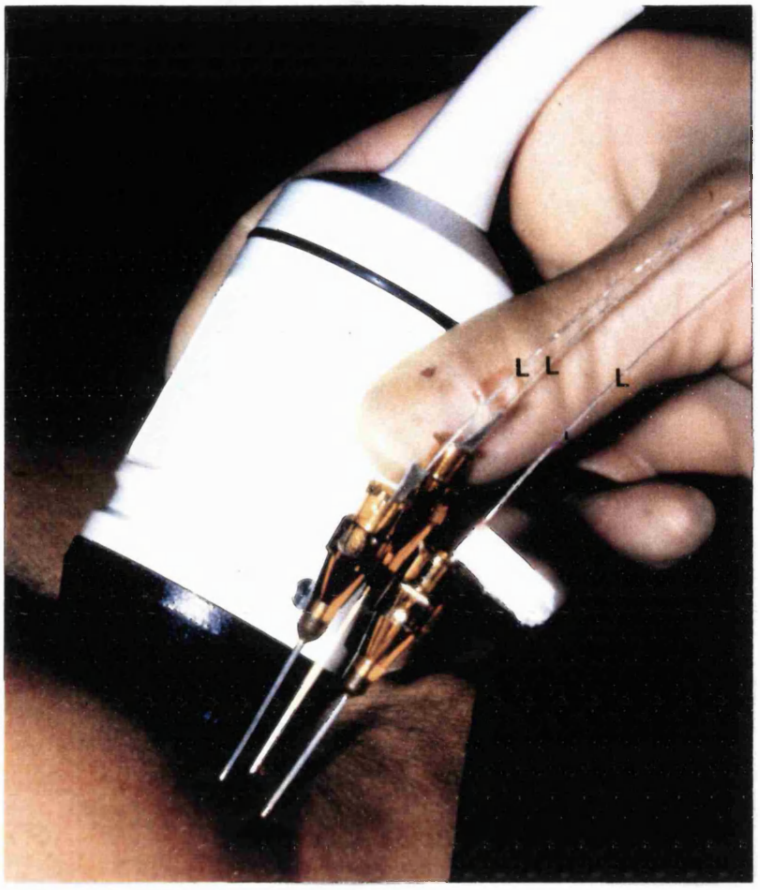


Figure 6.01. 3.5 MHz US transducer checking needle position. Note laser fibres (L) which have been inserted down each needle so that the tip lies within the tumour.

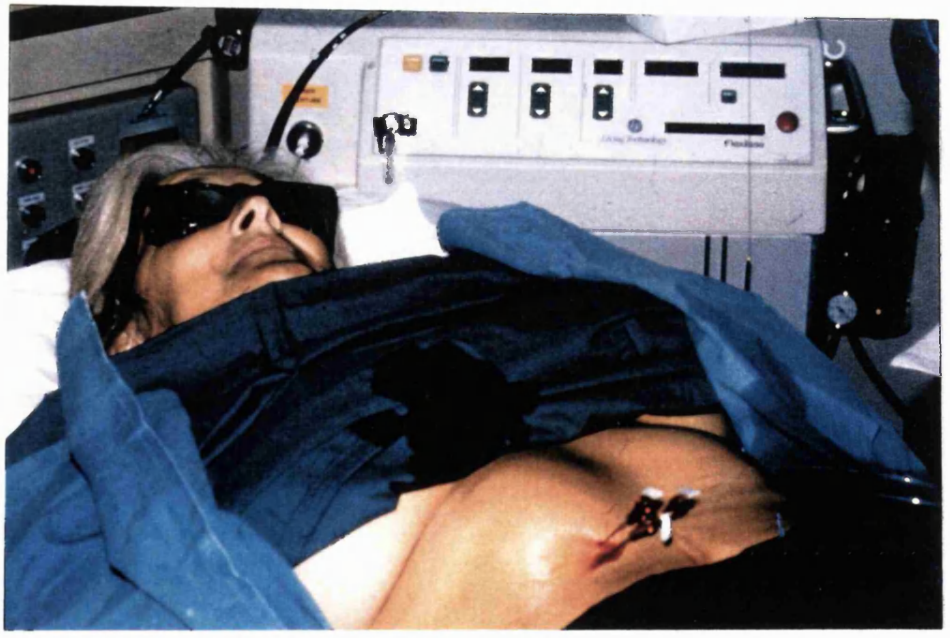


Figure 6.02. Patient with needles and fibres in position at the start of treatment. Note protective goggles and Nd:YAG laser in the background.

Gentamicin 80 mg 8 hourly). Venous access was maintained using a 17 gauge intravenous cannula. Monitoring consisted of sequential blood pressure, pulse rate, and respiratory rate estimations on a 3 minute cycle with continuous transcutaneous oxygen saturation monitoring. The abdominal wall was prepared and draped in a sterile manner. The intended puncture sites were then infiltrated down to the liver capsule with 10-15 ml of 1% solution of plain lignocaine. Core biopsy of the metastases were performed in 4 patients using a a spring loaded biopty instrument (Radiplast biopty, Henley medical supplies limited, London, UK) with an 18 gauge (1.2 mm diameter) biopty-cut biopsy needle (Bard urological division, CR Bard Inc, Covington, GA 30209) under US control. The preferred approach for needle insertion was subcostal rather than through the intercostal space to minimise tearing of the liver parenchyma due to relative fixity of the needles in the intercostal space. However, limitations of needle length (15cm) forced an intercostal approach on four occasions when treating small tumours located deep within the right lobe.

Three to four hollow 19 gauge needles (diameter 0.8mm) were inserted percutaneously into the most posterior aspect of the selected metastasis under US control (Figure 6.01). The needle tips were in juxtaposition with a separation of approximately 1.5 cm between individual needles to ensure treatment of all intervening tissue. A suitably prepared 200 micron fibre from a 1x4 200 micron star coupler was inserted down each needle such that 3-4 mm of bare silica core lay within the metastasis. Once a satisfactory placement was achieved, the laser was fired at the preset power for 500 seconds (Figure 6.02). The needles and fibres were then withdrawn by approximately 1.0 to 1.5 cm into a more anterior untreated portion of the metastasis and the laser fired again for a further 500 seconds. This process is repeated as many times as is necessary (usually 4) such that by the end of treatment a contiguous cylinder of tissue necrosis is 'cored' out through the tumour centre. For small metastases (diameter $\leq$ 3 cm), the extent of treated area overlapped into normal liver. Larger metastases required further needle and fibre manipulation to ensure a greater area of necrosis and incorporation of the tumour edge into the treatment zone. The evolving thermal changes occurring at the treatment sites were monitored in real time by US. On return to the ward, the patients were closely observed for signs of intraperitoneal bleeding. The following day, repeat haematological and biochemical screens were

performed in conjunction with a full clinical assessment. All patients were discharged within 24 hours of treatment.

Follow up contrast enhanced CT scans were performed in 12 patients at a mean time of 13 weeks from treatment (range 2 to 36 weeks). Those scans performed relatively late were early in the course of this study. In addition, 3 patients had CT scans performed 24 hours following treatment. The time intervals initially selected were to a certain extent arbitrary although for some patients living abroad or without easy access to transport, then logistical constraints dictated follow up and retreatment intervals. However, early on in the study, extensive real time and final US changes seen in treated tumours initially lead us to believe that complete tumour necrosis had been easily achieved. Subsequent follow up with CT revealed evidence of tumour progression rather than regression. This prompted a reduced follow up interval so that assessment and further treatment could be planned earlier. Post treatment scanning consisted of contiguous 8 mm sections through the liver immediately following bolus injection of 100 ml of non-ionic contrast with a further 50 ml during scanning. If post treatment CT scans showed residual viable tumour, patients were retreated within 2 to 4 weeks. If no residual tumour was identified, a CT scan was repeated at 2 to 3 months looking for any evidence of tumour recurrence. The treatment goal in those individuals with large tumours was to debulk and prevent tumour growth rather than achieve complete eradication. This explains the long treatment interval (up to 36 weeks) in some patients. Liver biopsies were performed in 4 patients at a range of times (3 to 36 weeks) following treatment. Where appropriate, tumour marker assays were requested.

6.3 ASSESSMENT OF RESULTS

The extent of laser induced necrosis was assessed by comparing the enhancement pattern for a given metastasis on dynamic pre and post-treatment CT scans. These were found to be more useful than non-contrast and delayed scans. Areas of total non-enhancement which previously enhanced were considered avascular and therefore necrotic as a result of treatment. Conversely, enhancing areas were taken to indicate residual viable tumour. The volume of all metastases and regions of non enhancement were assumed to be roughly spherical and calculated from the formula $4/3\ \Pi r^3$. The radius r was calculated as

the mean of the radii in the x, y and z axis. The volume of necrosis was then expressed as a percentage of the metastasis volume on the follow up scan. Accurate comparative measurement of tumour necrosis volume was not possible due to irregular margins of most tumours and areas of necrosis in addition to the influence of respiratory variation between scans. Metastases response to treatment was therefore graded according to the extent of necrosis in the following way :-

Grade I - 100% necrosis.

Grade II - > 50% necrosis but < 100%.

Grade III - < 50% necrosis.

Average metastases and necrosis volumes, percentage necrosis and necrosis grades are tabulated in Appendix I.

6.4 RESULTS

Patient details, number and average metastases diameters, necrosis grades and survival from treatment are summarised in Appendix II. A total of 52 treatment sessions were performed in 12 patients with 33 metastases. The average number of metastases per patient was three (range 1-8). Two metastases exceeded a diameter of 6.0 cm with a mean metastasis diameter of 3.5 cm (range 1 -11 cm). Thirty one metastases were less than or equal to 6 cm, 18 metastases were less than or equal to 3.0 cm and 2 metastases measured 5 and 11 cm. Absolute and mean metastatses diameters are presented in Appendix III. The mean duration of treatment per patient was 9 months (2.5 to 20 months). There were 60 tumour treatments.

Mean interval from resection of the primary cancer to first laser treatment was 30 months (range 5 to 108 months). Five patients had synchronous metastases at the time of resection, the remainder had developed metachronous lesions; 5 patients had previous chemotherapy for their hepatic tumours. Details of patients receiving chemotherapy and its relationship to laser treatment is presented in Appendix IV. Only 4 of the 12 patients had a confirmed histological diagnosis of hepatic metastases before treatment. Follow up histology was available in 5. A total of 41 CT scans were performed for treatment assessment. Eleven scans were carried out within 24 hours of treatment with the remaining

30 undertaken at a mean interval of 10 weeks from treatment (range 2-28 weeks). A total energy of nearly 600,000 joules was used in the 52 treatments giving an average number of joules per treatment of 11,526 joules (range 2,700-35,000 joules). The average total treatment energy per patient was 46,105 joules (range 8,000-133,160 joules).

6.4.1 ULTRASOUND

Prior to treatment, all metastases on US invariably had a mixed echogenic appearance sometimes with central areas of dystrophic calcification (Figure 6.03a). Sonographic monitoring of the evolving thermal changes in real time showed a characteristic pattern. Within 100 seconds of commencing photocoagulation, a bright relatively well defined hyperechogenic area developed around each of the fibre tips due to fluid vaporisation and microbubble formation (Figure 6.03b). As photocoagulation progressed, the extent of each hyperechogenic area increased becoming confluent with that developing around adjacent fibres. Echogenic linear striations were often seen radiating from the treatment area and probably represent conduction of heat and microbubbles along tissue planes. Cellular water vaporised and could be seen as bubbles emanating from around the fibre tips embolising into adjacent venous radicles. This produced no overt clinical problems. By the end of 500 seconds of treatment, a relatively well defined confluent hyperechogenic area centred around the fibre tips had replaced the previous mixed echogenic pattern (Figure 6.03c). The extent of these changes are thought to represent the treated tumour volume. For large metastases, this transformation allowed clear delineation between treated and non-treated areas. At subsequent follow up (greater than 2 weeks), there were no specific sonographic features distinguishing viable and necrotic tumour.

6.4.2 CT SCANS

All metastases on contrast enhanced CT scanning appeared as areas of low enhancement compared to the normal hepatic parenchyma. Large metastases (diameter > 3cm) invariably had a central zone of non-enhancement suggestive of spontaneous central necrosis or cystic degeneration (Figure 6.04a). Dystrophic calcification was noted in the

Figure 6.03a

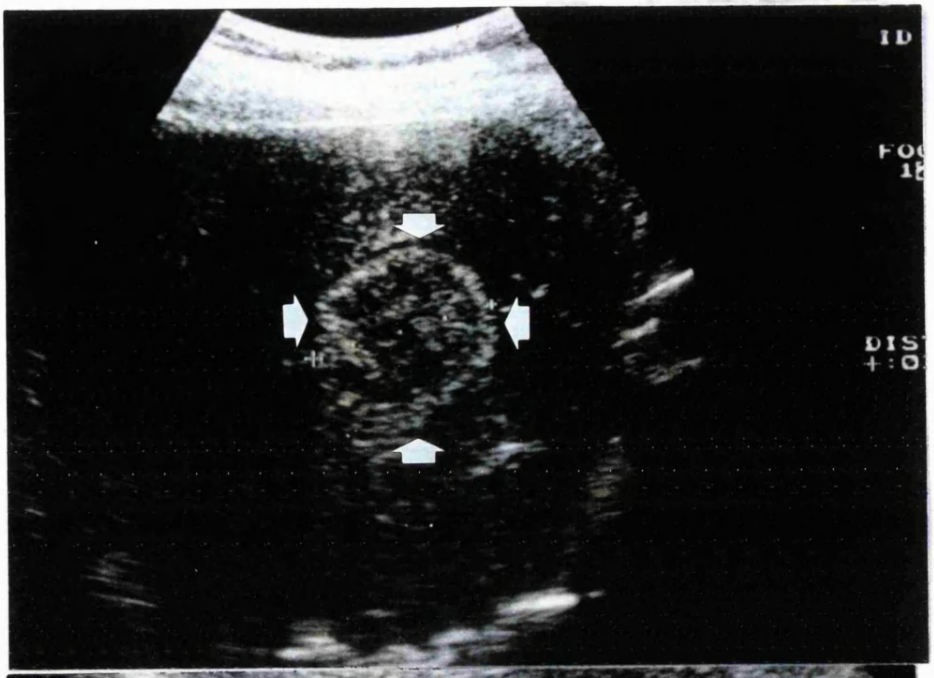


Figure 6.03b

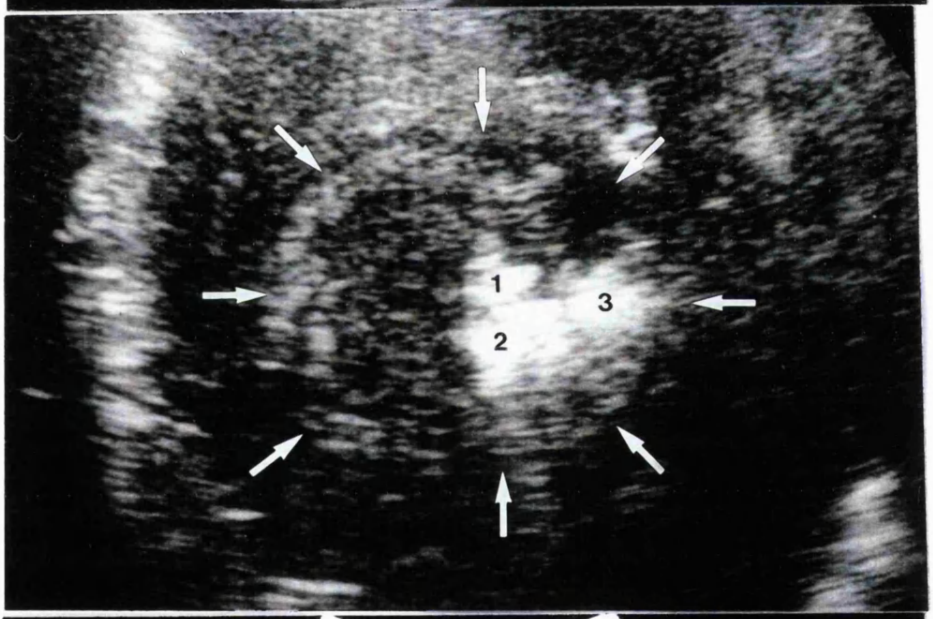


Figure 6.03c

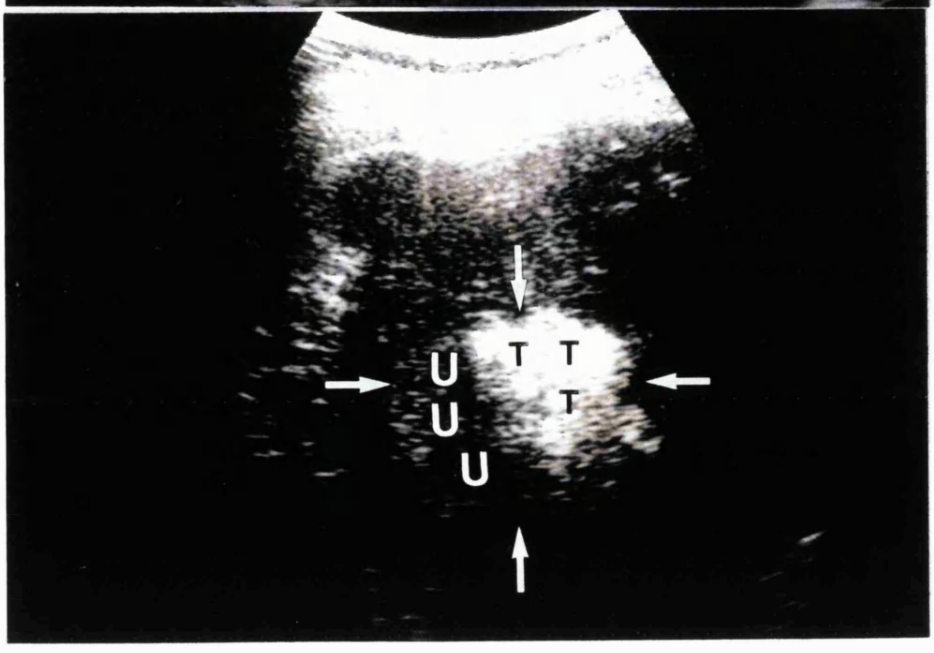


Figure 6.03a. US appearance of a 4 cm diameter mixed echogenic colorectal metastasis (arrowed) prior to treatment.

Figure 6.03b. The same lesion (arrowed) halfway through a 500 second exposure at a power of 2.0 watts per fibre. There are three hyperechogenic foci (numbered) each developing around one of the three fibres used.

Figure 6.03c. The same metastasis (arrowed) immediately at the end of treatment. There is a well defined hyperechogenic area occupying the right half of the lesion with clear demarcation between treated (T) and untreated (U) portions.

centre of 3 colorectal metastases. Following treatment, the CT features of metastases varied from complete non-enhancement of the whole tumour (Figure 6.04a & b) to smaller areas of non-enhancement with surrounding viable tumour (Figure 6.05a & b). Subsequent rescanning of retreated viable tumour areas confirmed non-enhancement (Figure 6.05c & d).

All metastases treated showed radiological evidence of at least partial necrosis. Of the 33 metastases treated, 70% (n=23) showed necrosis in 50% or greater of tumour volume. Twenty five percent (n=8), 45% (n=15) and 30% (n=10) achieved necrosis grades of I, II and III respectively (Table 6.02).

NECROSIS GRADE	*NO. OF METASTASES*	*MEAN DIAMETER (CM)*
I	*8 (25%)*	*2.0 (1.5-3.0)*
II	*15 (45%)*	*3.0 (1.0-4.0)*
III	*10 (30%)*	*6.0 (4.0-11.0)*

TABLE 6.02. Number of metastases and their respective necrosis grades.

Fifty five percent (n=18) of metastases were ≤ 3 cm in diameter with 45% (n=15) had a diameter > 3 cm. Table 6.03 compares the extent of necrosis in these two groups.

DIAMETER (CM)	*METASTASIS NUMBER*	*NECROSIS GRADE I*	*NECROSIS GRADE II*	*NECROSIS GRADE III*	*TREATMENT NUMBER*
≤ 3.0	*18 (55%)*	*8 (44%)*	*10 (56%)*	*0*	*23*
> 3.0	*15 (45%)*	*0*	*5 (33%)*	*10 (67%)*	*37*

TABLE 6.03. Necrosis grades for small and large metastases.

Of the 18 metastases ≤ 3 cm in diameter, 44% (n=8) and 56% (n=10) exhibited necrosis grades of I and II respectively. There were no grade III responders. Conversely, of the 15 metastases > 3 cm in diameter, 33% (n=5) and 67% (n=10) exhibited necrosis grades of II and III respectively. There were no grade I responders. The impression is that small metastases display the greatest extent of necrosis with mean diameters of 2 cm, 3 cm

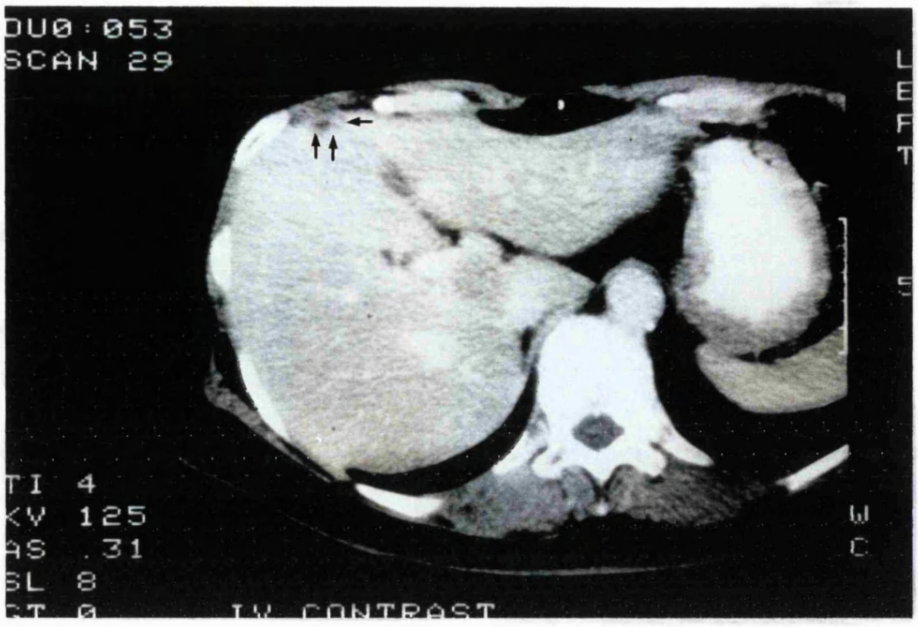


Figure 6.04a. A contrast enhanced CT scan of a poorly enhancing 2 cm metastasis (arrowed) in the superficial portion of the right lobe.

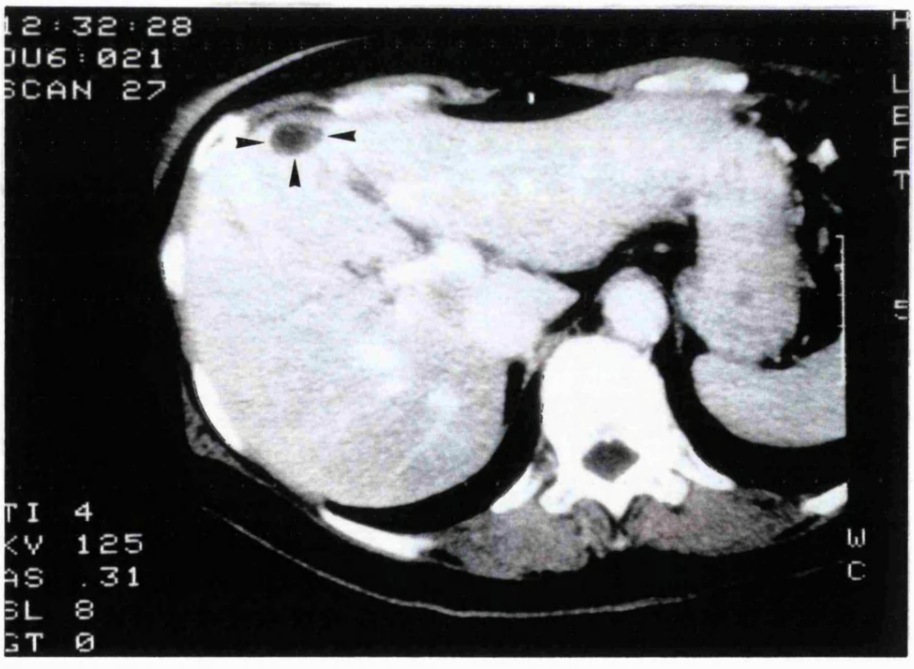


Figure 6.04b. The same lesion 24 hours from treatment. The change in its enhancement pattern is consistent with total tumour necrosis.

and 6 cm for lesions achieving necrosis grades of I, II and III respectively (Table 6.02). Despite roughly equal numbers of small and large tumours, the number of treatments required for the latter is much higher (37 versus 23) with a poorer outcome (Table 6.03).

6.4.2.1 CT SCANS AT 24 HOURS

Seventeen metastases which had received 26 tumour treatments were scanned within 24 hours of treatment. Eighty nine percent (n=15) exhibited necrosis in 50% or greater of their respective volumes. Of the 17 tumours treated, 30% (n=5), 59% (n=10) and 11% (n=2) showed necrosis grades of I, II and III respectively (Table 6.04).

NECROSIS GRADE	*NO. OF METASTASES*	*MEAN DIAMETER (CM)*
I	*5 (30%)*	*2.0 (2.0-3.0)*
II	*10 (59%)*	*3.0 (1.0-4.0)*
III	*2 (11%)*	*6.0 (5.0-6.0)*

TABLE 6.04. Number of metastases and their respective necrosis grades.

Sixty five percent (n=11) of metastases scanned within 24 hours were ≤ 3.0 cm in diameter with 35% (n=6) > 3.0 cm. Table 6.05 compares the extent of necrosis in the two groups.

Diameter (cm)	*Metastasis Number*	*Necrosis Grade I*	*Necrosis Grade II*	*Necrosis Grade III*	*Treatment Number*
≤ 3.0	*11 (65%)*	*5 (45%)*	*6 (55%)*	*0*	*12*
> 3.0	*6 (35%)*	*0*	*4 (67%)*	*2 (33%)*	*14*

TABLE 6.05. Necrosis grades for small and large metastases.

Of the 11 metastases ≤ 3.0 cm in diameter, 45% (n=5) and 55% (n=6) were grade I and II responders respectively. There were no grade III responses. Conversely, of the 6 metastases > 3.0 cm in diameter, 67% (n=4) and 33% (n=2) were grade II and III responders. There were no grade I responses. Despite the small absolute numbers, it would

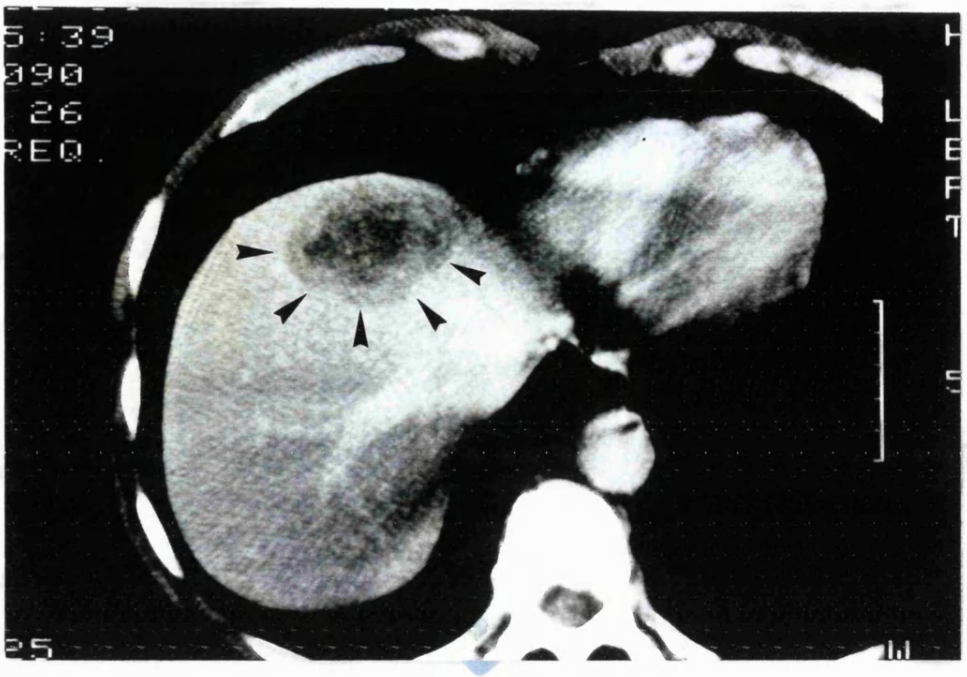


Figure 6.05a. A contrast enhanced CT scan showing a poorly enhancing 5 cm metastasis (arrowed) in the right hepatic lobe prior to treatment. A non-enhancing central portion is suggestive of cystic degeneration.

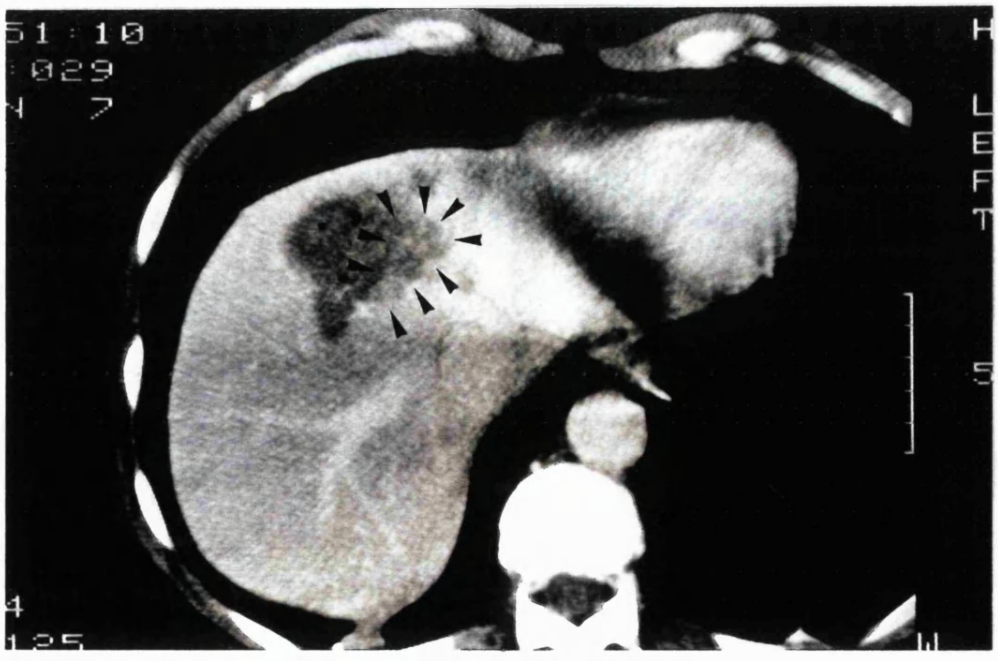


Figure 6.05b. The same lesion 24 hours from laser treatment. The black spots represent gas in the tissues with the lateral aspect showing non-enhancement. A poorly enhancing rim on the medial side is suggestive of viable residual tumour.

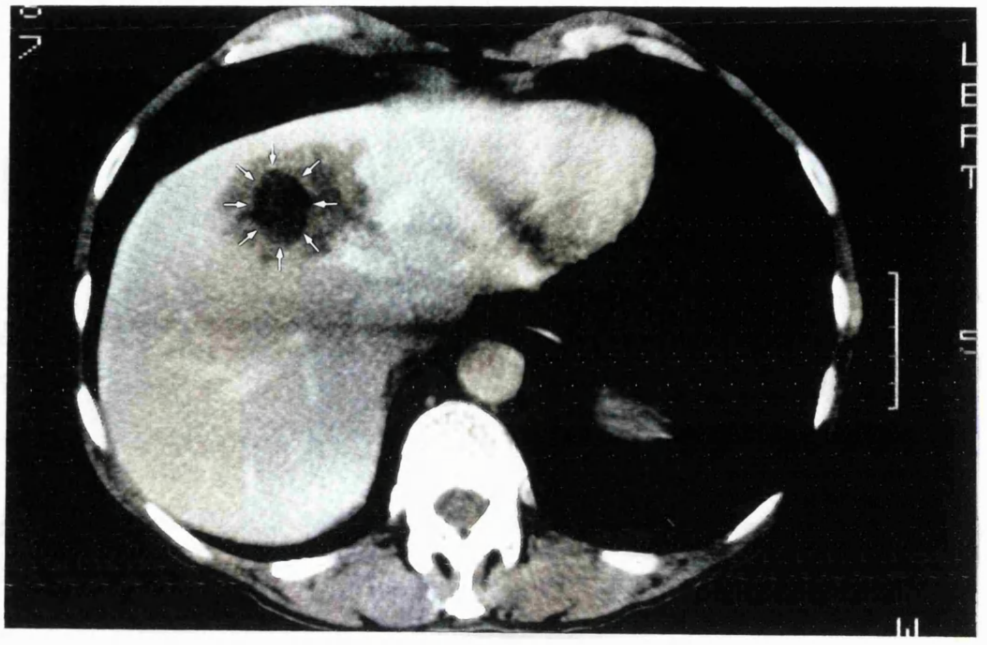


Figure 6.05c. Four weeks from treatment, there is a central non-enhancing area of non-viable tumour (arrowed). A circumferential rim of poorly enhancing tissue represents residual tumour prompting further treatment.

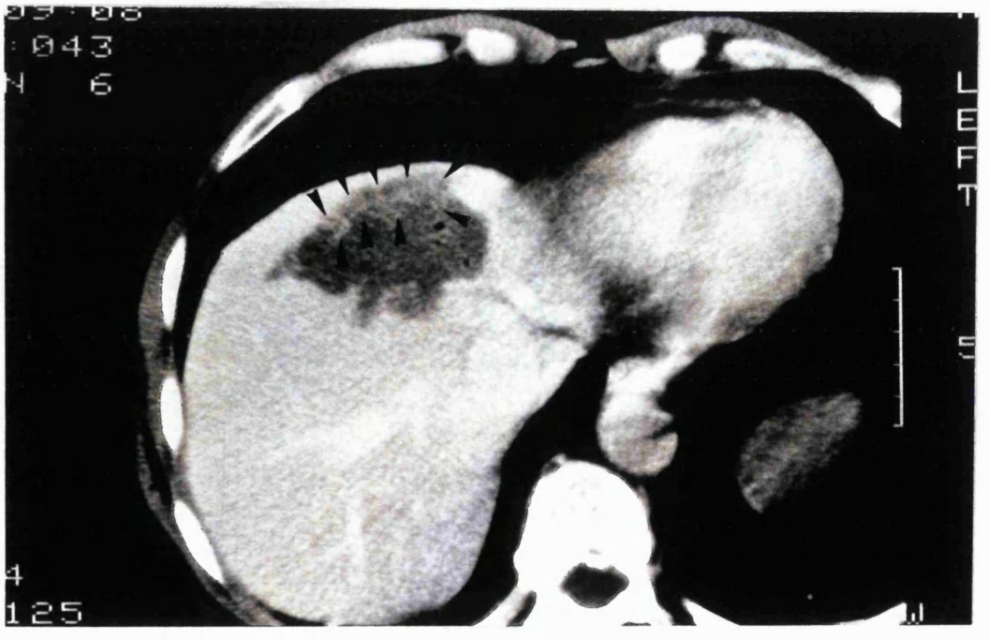


Figure 6.05d. 24 hours following a second laser treatment, there is gas in the medial aspect of the tumour suggestive of further tumour necrosis. With the exception of the anterior portion (arrowed), the enhancing pattern suggests little residual viable tumour.

seem that small metastases are more sensitive to the effects of laser hyperthermia with a mean metastasis diameter of 2.0, 3.0 and 6.0 cm for necrosis grades I, II and III respectively (Table 6.04). The number of treatments (Table 6.05) was comparable for the two groups yet better results were achieved in nearly twice as many small as large metastases.

6.4.2.2 CT SCANS LATER THAN 24 HOURS

Sixteen metastases which had received 34 tumour treatments were scanned at various time intervals from treatment (mean 10 weeks, range 2-28 weeks). Fifty percent of tumours exhibited necrosis in 50% or more of their respective volumes. Of the 16 metastases treated, 19% (n=3), 31% (n=5) and 50% (n=8) showed necrosis grades of I, II and III respectively (Table 6.06)

NECROSIS GRADE	*NO. OF METASTASES*	*MEAN DIAMETER (CM)*
I	*3 (19%)*	*1.5 (1.5-2.0)*
II	*5 (31%)*	*3.0 (1.5-4.0)*
III	*8 (50%)*	*6.0 (4.0-11.0)*

TABLE 6.06. Number of metastases and their respective necrosis grades.

Forty four percent (n=7) of metastases scanned later than 24 hours from treatment were ≤ 3.0 cm in diameter with 56% (n= 9) > 3.0 cm. Table 6.07 compares the extent of necrosis in the two groups.

DIAMETER (CM)	*METASTASIS NUMBER*	*NECROSIS GRADE I*	*NECROSIS GRADE II*	*NECROSIS GRADE III*	*TREATMENT NUMBER*
≤ 3.0	*7*	*3 (43%)*	*4 (57%)*	*0*	*11*
> 3.0	*9*	*0*	*1 (11%)*	*8 (89%)*	*23*

TABLE 6.07. Necrosis grades for small and large metastases.

Of the 7 metastases ≤ 3.0 cm in diameter, 43% (n=3) and 57% (n=4) exhibited necrosis grades of I and II respectively with no grade III responders. Conversely, of the 9 metastases > 3.0 cm in diameter, 11% (n=1) and 89% (n=8) showed necrosis grades of II and III respectively with no grade I responses. Although the numbers are small, the impression is that small metastases respond better to treatment. The mean metastasis diameters are 1.5, 3.0 and 6.0 cm for necrosis grades I, II and III (Table 6.07). The numbers of small and large metastases are comparable yet the latter group received twice as many treatments as the former with poorer results (Table 6.07)

Over the period of the study, treated metastases remained as well defined non enhancing regions for 2 to 4 month interval from treatment. This was invariably followed by relentless tumour progression despite further laser treatment. In no patient was there any convincing evidence of tumour regression or disappearance despite varying degrees of demonstrable laser induced necrosis. Tumour progression bore no clear relationship to the necrosis grade achieved.

6.4.3 TUMOUR MARKERS

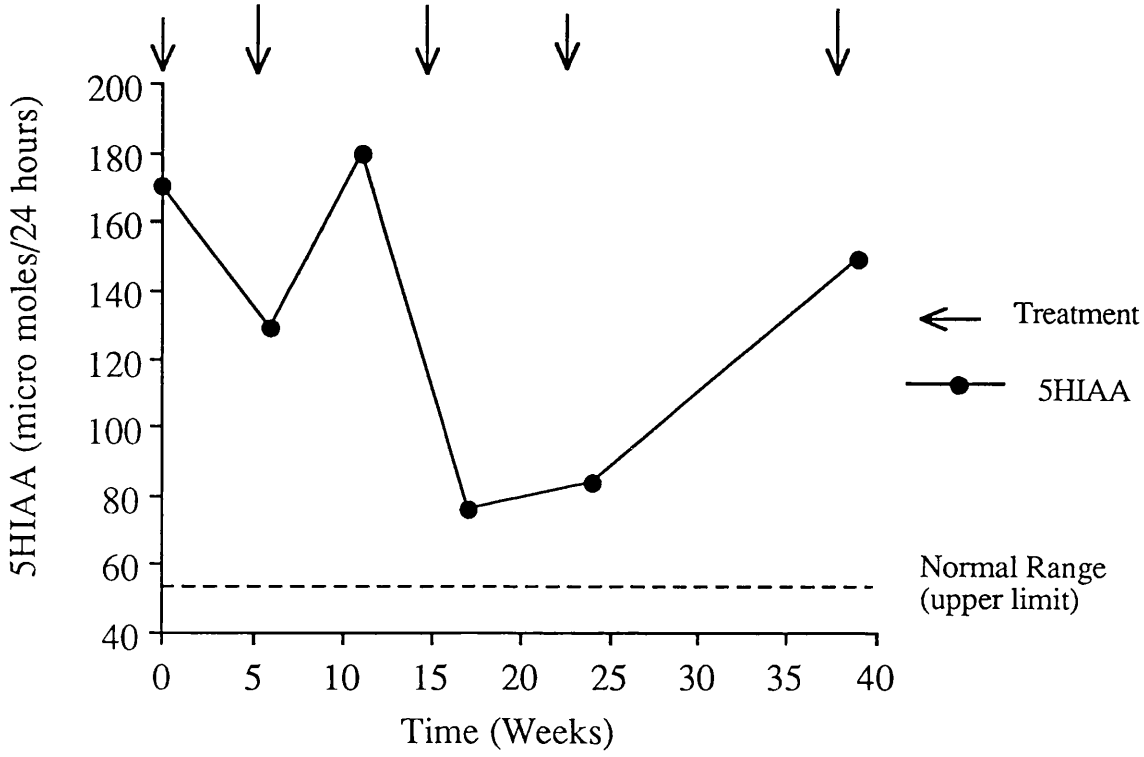
Serum Carcino-embryonic antigen (CEA) titres were measured before and after treatment in 6 patients with colorectal hepatic metastases. A patient with carcinoid hepatic metastases had regular 24 hour urinary 5-Hydroxy Indole Acetic Acid (5-HIAA) measurements.

CEA titres rose relentlessly in all patients throughout the treatment duration (Appendix V). However, 5-HIAA levels fell from a pre-treatment level of 170 micromoles/24 hours to a low of 76 micromoles/24 hours following two treatments. Fourteen months and five treatments later the 5-HIAA level is no higher than its initial level (Graph 6.01).

6.4.4 HISTOLOGY

Four ultrasound guided liver biopsies were performed in 4 patients at a mean follow up of 8 weeks from the last treatment (range 3 to 16 weeks). In 2 patients, adenocarcinoma cells consistent with spread from a colorectal primary were seen. Acute inflammation and

intense fibrosis with no evidence of malignancy were reported in the remaining 2 patients (Figure 6.06a & b).



GRAPH 6.01. Relationship of urinary 5HIAA to laser therapy.

There seemed no obvious relationship between the biopsy result and the extent of necrosis achieved in the sampled metastasis. Those metastases with histologically proven residual tumour were thought to harbour viable tumour on follow up CT i.e did not achieve grade I necrosis.

6.4.5 LONG TERM FOLLOW UP

Of the 12 patients, 7 have been followed up for 14 months or longer from initial laser treatment; the remaining 5 were followed up for between 4 and 8 months.

At the time of writing, 8 patients have since died at a mean interval from first laser treatment of 17 months. Four patients have died from multiple hepatic metastases with no clinical evidence of extrahepatic disease at a mean treatment interval of 20 months from initial treatment. Another patient succumbed 4 months from treatment to extensive intra-abdominal disease in the presence of an enlarging solitary hepatic metastasis. The last 3

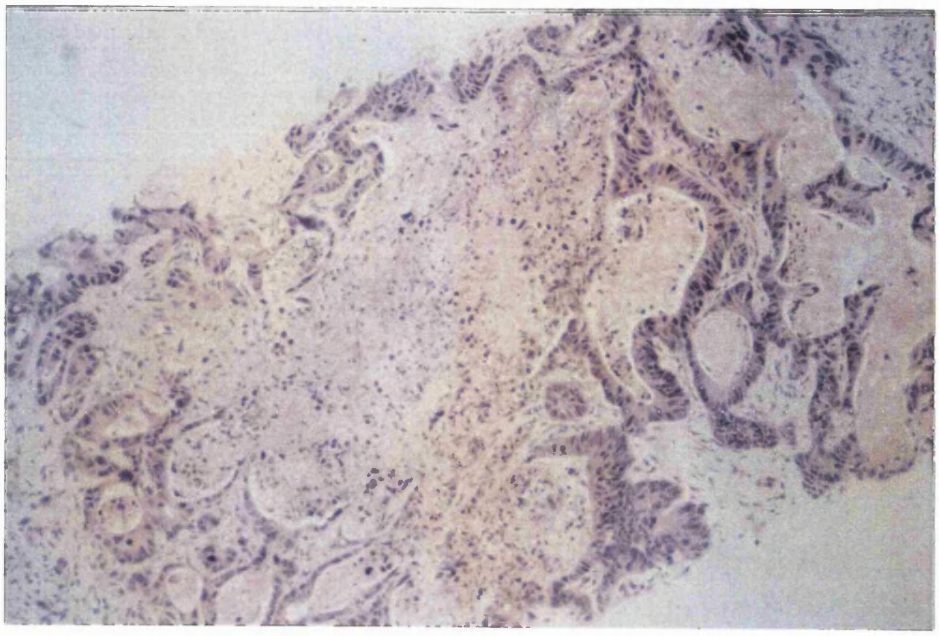


Figure 6.06a. A low power view of a core biopsy of a hepatic lesion. The normal liver architecture is replaced by adenocarcinoma consistent with a colonic primary (H&E stain).

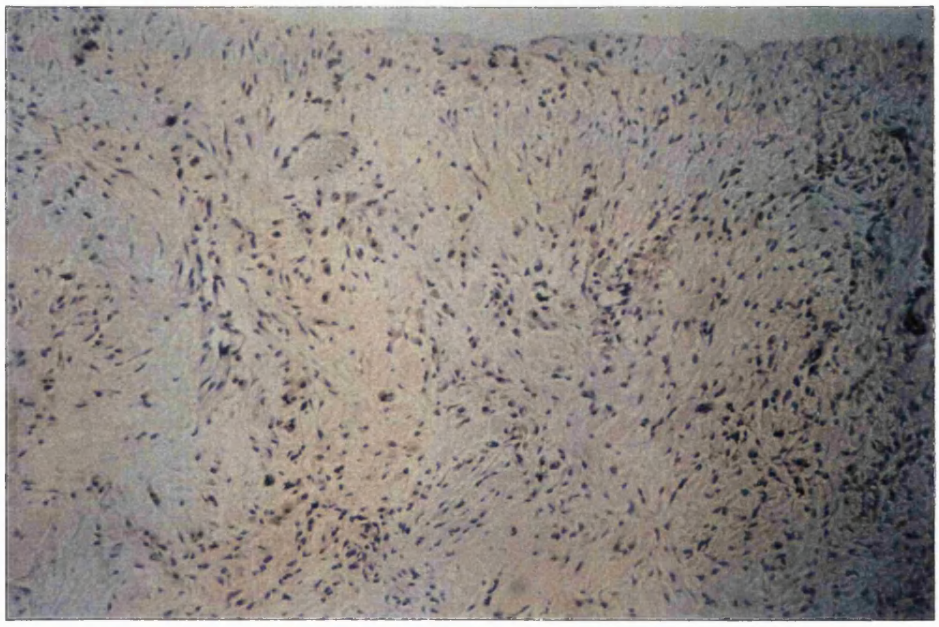


Figure 6.06b. Repeat biopsy 8 weeks from treatment shows extensive fibrosis with no viable tumour (H & E stain).

patients died from extensive pulmonary disease with several expanding hepatic metastases at a mean treatment interval of 16 months from initial treatment.

Of the remaining 4 patients currently alive, 2 are receiving chemotherapy for enlarging hepatic metastases. Pulmonary metastases are present in one of the two patients. One asymptomatic patient is receiving no further laser treatment for enlarging hepatic metastases as the tumours have attained a size where laser treatment is unlikely to provide any worthwhile tumour regression. The remaining patient has developed recurrent pelvis disease and further laser treatment has been halted while surgical treatment of the recurrence is underway.

Mean overall survival time from initial laser treatment was 20 months (4-40 months). Six patients (50%) have survived 26 months or longer from initial treatment, 2 (17%) and 3 patients (25%) have lived for at least a year and 6 months or more respectively. One patient (8%) survived for less than 6 months. Absolute survival in months for individual patients from initial laser treatment are summarised in Appendix II.

6.4.6 COMPLICATIONS

Most patients described mild to moderate abdominal wall pain at the puncture sites. This resolved spontaneously within 48 to 72 hours of treatment in most instances and rarely required more than mild oral analgesia for relief.

A patient developed a hepatic subcapsular haematoma noted 3 weeks from treatment. This resolved spontaneously. A CT scan in another patient 24 hours following treatment of a small deep seated tumour in the right lobe showed a perinephric and intrarenal haematoma of the right kidney. The patient had no macroscopic haematuria although did complain of some back and right loin pain. No specific treatment was necessary.

A vaso-vagal response was noted in one patient attributable to stimulation of the vagal plexus on a large blood vessel near the treatment site. This responded appropriately to intravenous atropine. Another patient complained of shoulder tip pain probably due to stimulation of the diaphragmatic peritoneum when treating a metastasis high under the dome of the diaphragm.

In none of the patients was there any evidence of secondary haemorrhage, haemobilia, bile leakage or sepsis within the liver. This is despite a two to three fold rise in aspartate transaminase noted within 24 hours of treatment indicative of normal parenchymal necrosis in over 50% of treatments where measured (n=28)

6.5 DISCUSSION

The palliative management of hepatic metastases remains unsatisfactory. A need remains for a simple and safe technique for controlling local tumour growth, although what influence this has on survival is not clearly known. Given that survival is related directly to the extent of hepatic replacement by tumour, then attempts to reduce viable tumour load would seem a worthwhile goal.

Ultrasound proved invaluable in laser therapy of hepatic metastases. It was possible to confirm number, site and size of metastases seen on pre treatment CT scans in addition to detecting missed lesions in 2 patients. Ultrasound provided important information on the spatial relationship of metastases to important vascular and biliary radicles thereby avoiding their inadvertent damage during treatment. Demonstration of flow in large blood vessels adjacent to treatment areas confirmed their patency. In experienced hands, relatively precise needle placement within a metastasis and relative to each other was possible. However, small tumours ($\leq$ 3.0 cm in diameter) located deep and either inferiorly or superiorly within the right lobe posed a considerable challenge.

For small metastases, real time US imaging revealed a hyperechogenic region which completely replaced the pre-treatment mixed echogenic or hypoechogenic appearance. For large tumours, it was often possible to distinguish between treated and untreated tumour portions (Figure 6.03). However, distortion of the US image by a hyperechogenic signal arising from previously treated sites could make identification of viable tumour and subsequent fibres position difficult. Thus, intervening areas of viable tumour could escape treatment leading to early recurrence.

It is interesting to note that real time sonographic images of tumours treated using ILH were very similar to those obtained when treating normal canine liver. This is despite marked differences in the optical characteristics of normal liver and tumour. In the former,

experimental work has confirmed the extent of sonographic changes correlate accurately with the macroscopic extent of tissue necrosis 5 to 7 days from treatment (Steger et al., 1992). Judging by the areas of non-enhancement on CT shortly following treatment, the hyperechogenic area may be reliable in predicting the true extent of tumour necrosis. However, despite what appeared to be complete tumour necrosis in several instances on follow up CT scans, none of the 33 metastases treated regressed or disappeared. While it is conceivable that treatments were incomplete or poorly targeted, a question mark must remain over the real significance of the real time US changes as accurate indicators of the nature and extent of tumour necrosis. This point will be considered further on in the discussion.

Dynamic CT imaging following intravenous contrast administration depends on increased enhancement of normal liver parenchyma compared to that of the tumour due to the relatively poor vascularity of the latter. Similarly, assessment of the extent of laser induced necrosis relies on differences in attenuation between viable and non-viable tissue. This occurs maximally 2 to 3 minutes following injection. Prior to treatment, some metastases exhibit areas of cystic degeneration or spontaneous necrosis which appear as non-enhancing zones. This emphasizes the importance of scanning patients as close to before a treatment as possible to avoid attributing such changes to laser treatment. Delayed scans were also performed because some hypervascular metastases become iso-attenuating to normal liver parenchyma during dynamic contrast enhancing CT scan. Dynamic CT was more valuable than pre-contrast or delayed scans in delineating the extent of laser induced necrosis. These appeared as well defined non-enhancing areas of variable shape. Distinguishing between non-enhancing treated and viable tumour was relatively easy. However, the significance of an enhancing ring which often appeared around a tumour several weeks from treatment is unclear. This may represent acute inflammatory oedema, regenerating liver or recurrent tumour.

On the basis of follow up CT scans, all 33 metastases showed radiological evidence of at least partial necrosis. The distribution of small (diameter $\leq$ 3.0 cm) and large metastases (diameter > 3.0 cm) was roughly equal (18 versus 15). Seventy percent (n=23) of metastases treated exhibited necrosis in 50% or more of their respective volume (grade I

or II). All small metastases showed either grade I or II necrosis. However, only one third of large metastases achieved grade II necrosis with none showing grade I response. It seems reasonably clear that small metastases are more susceptible to the effects of laser therapy. The mean metastasis diameter for grade I, II and III was 2.0, 3.0 and 6.0 cm respectively lending further support to this notion. The number of laser treatments was significantly lower for small compared to large metastases (23 versus 37) yet the results for small metastases are clearly better. However, this difference may be less significant as the laser energy per treatment varied considerably.

A possible explanation for superior results obtained with small metastases lies with the volume of tumour necrosis that can be achieved using a 4 fibre system. Experimental studies in normal liver demonstrated that tissue necrosis up to 4 cm in diameter can be achieved reliably (Steger et al., 1992). Assuming that differences in the optical properties of normal and tumour tissue do not influence the diameter of necrosis and that fibre position were uniformly optimal then, the volume of necrosis achieved using a 4 fibre system "covers" the volume of a 3 cm tumour with ease. For larger metastases, several manipulations of the laser fibre are necessary to achieve sufficient tumour necrosis. Errors in needle placement are inevitable so that intervening areas of viable tumour between successive treatment sites may go unrecognised and escape treatment.

Despite an apparently generous "overkill" margin for small metastases, of the 18 metastases $\leq$ 3.0 cm in diameter, only 44% (n=8) were grade I responders with the remaining 56% (n=10) grade II responders. Other factors may therefore be at play include tumour inaccessibility, poor needle placement, variation in tumour vascularity and time interval from treatment to assessment. Small inaccessible tumours in the right lobe make precise placement and separation between individual needles difficult so that viable tumour maybe left at the end of treatment. Hypervascular metastases may produce unfavourable temperature gradients due to cooling effect of flowing blood. Therefore, identical laser parameters applied to tumours of similar volume may produce differences in necrosis volumes.

One problem was deciding the time interval from treatment to follow up CT scan. Initially, logistical constraints prevented early treatment assessment. However, realising

that the window of opportunity for imaging the extent of necrosis at a maximum was likely to occur within a relatively short time of treatment, thus our follow up protocol was modified to take this factor into account. Imaging patients relatively late may underestimate the extent of laser induced necrosis due to tissue resorption and healing. If this indeed was the case, then one might expect superior imaging results in those metastases scanned within 24 hours of treatment. Seventeen metastases were scanned within 24 hours of treatment (group A) compared to 16 which were scanned later (group B). Eighty nine percent (n=15) of tumours in group A exhibited necrosis in 50% or greater of their respective volumes compared to a figure of 50% (n=8) in group B leaving 11% (n=2) and 50% (n=8) in group A and B respectively as grade III responders. The mean metastasis diameter in groups A and B for necrosis grades of I (2.0 cm), II (3.0 cm) and III (6.0 cm) were the same. This may suggest that early scanning as in group A detects the extent of necrosis at its maximum rather than a preponderance of large metastases in group B as the cause. However, the mean metastasis diameter in groups A and B are misleading. The distribution of small and large metastases in both groups varies significantly with 65% (n=11) and 44% (n=7) as small metastases in groups A and B respectively. The figures for large metastases are 35% (n=6) and 56% (n=9) for group A and B respectively. The superior results in group A could be due to a preponderance of of small metastases rather than early scanning. A further explanation is that the apparent extent of necrosis seen at 24 hours is optimistically misleading and that viable tumour remains. Given that, later scanning may provide a more accurate assessment of what laser treatment has actually achieved.

The number of tumour treatments were 26 for group A and 34 for group B. The superior results for group A cannot therefore be attributed to a higher number of tumour treatments despite roughly equal number of tumours in the two groups. To assess the true significance of early scanning, several groups of metastases of a comparable size need to be scanned at various times (24 hours, 3, 7 days, 2, 4, 8 and 12 weeks) from treatment using identical laser parameters. A correlation of scan appearances at different times with the long term fate of what has happened to treated metastases would help evaluate the usefulness of early scanning as measure of true tumour necrosis.

Despite radiological evidence of tumour necrosis, serum CEA in patients with colorectal hepatic metastases continued to rise. Transient rises shortly following treatment might be expected as a result of tumour necrosis releasing CEA into the circulation. Despite measuring levels at various intervals from treatment, and even allowing for a long circulating half life of CEA, none of the patients demonstrated any fall in their CEA titres. This probably does not reflect treatment failure but is indicative of occult hepatic and extrahepatic disease at the time of treatment. In addition, selective treatment of metastases invariably allowed progression of others during treatment interval. Infact, 8 out of the 9 patients with colorectal hepatic disease have at the time of writing developed overt multiple hepatic and or extrahepatic disease illustrating the limitations of even the most modern imaging techniques in staging malignant disease. Applying any form of regional therapy to hepatic metastases without knowledge of the true disease extent will invariably lead to poor results. The inadequacies of current staging techniques and the high incidence of occult hepatic and extrahepatic disease in patients with liver disease suggests that adjuvant therapy needs to be combined with laser therapy. The latter could debulk macroscopic disease while the former deal with microscopic residual disease. Possible adjuvant techniques include immunotherapy, photodynamic therapy and chemotherapy. The latter is perhaps the most attractive given that hyperthermia enhances tumour sensitivity to chemotherapy without increased side effects.

A single patient with slow growing carcinoid metastases showed significant falls in the 24 hour urinary 5HIAA levels related to 3 treatments (Graph 6.01). This, combined with radiological changes would suggest successful induction of tumour necrosis and was mirrored by a reduction in frequency of troublesome diarrhoea. However, 2 other laser treatments on the same patient did not produce corresponding falls in 5 HIAA levels. A possible explanation is that only treatment to those carcinoid tumours which secrete 5 HIAA and therefore contribute to the urinary levels will affect titres. The slow growing and less malignant nature of this tumour makes it more amenable to effective debulking.

Histological assessment was possible in 4 patients with 2 demonstrating viable tumour at previous treatment sites. The remaining 2 showed acute inflammation and fibrosis. Follow up CT in all 4 patients was thought to show residual viable tumour. While

encouraging, some care is needed in interpreting such limited data.The biggest pitfall must be sampling error especially in the case of small tumours. To biopsy the correct area under US control some weeks following treatment with no marker of the treatment site is difficult. This could be overcome by injecting a sonographic marker such as gelfoam into the treatment area upon completion. Gelfoam disappears 4 to 6 weeks following injection and therefore would not obscure the tumour if subsequent retreatment is necessary. Inaccurately targeted biopsy of tumour which is found to be necrotic could just as easily have arisen due spontaneous necrosis. With the exception of the presence of charring, reliable histological distinction between laser induced and spontaneous necrosis is not possible. In addition, biopsy of laser induced necrotic tumour will not identify viable residual tumour which on CT images may have been confidently predicted as necrotic. Finally, inadvertent biopsy of treated normal liver adjacent to a tumour will show similar features to treated tumour i.e fibrosis with no tumour. This may lead one to conclude erroneously that a metastasis has been successfully treated.

The two notable early complications include a hepatic subcapsular haematoma and an intrarenal / perinepheric haematoma in different patients. Both represent wayward needle placement despite US control and resolved spontaneously with no untoward clinical manifestation. The incidence of such problems is likely to improve with increasing experience or alternatively, CT or MRI may be used for greater precision of needle placement. The remaining problems were self limiting and of a minor nature. This inherent safety of ILH is likely to enhance its attraction to patients and clinicians alike.

Did laser treatment have any influence on disease progression ? In the absence of a controlled trial, any conclusions drawn from this study must be treated with some caution especially as some patients had received chemotherapy before, during and after treatment. All 12 patients have developed either multiple hepatic or pulmonary metastases or a combination of both. A total of 8 patients have died at a mean follow up of 17 months. The 1 year and 2 year survival figures were 75% and 50% respectively. While laser treatment in these patients may have produced at least partial necrosis of hepatic metastases, the influence on survival seems to have been negligible due to the presence of extensive occult disease from the outset. However, one must not ignore the possibility that laser treatment

may have induced or potentiated such an unfavourable state. Tumour cells are continuously embolising into the circulation. It is conceivable that as heat is dissipated from the fibre tips to the tumour periphery, a reactive hyperaemia occurs with dilatation of tumour and normal vessels. This may propagate tumour cell embolisation to other regions of the liver or from the liver to the lungs. Another possibility is stimulating compensatory growth of occult extrahepatic disease having achieved adequate local control of hepatic metastases. This phenomenon has been seen following regional chemotherapy for liver metastases.

What of the future of ILH ? Several problems need to be addressed. The first concerns US imaging. An important limitation is its resolution. relatively large tumours (diameter 1-2 cm) can be reliably detected. However, the correlation between the sonographic limits of a hepatic metastasis and its true extent is not clearly known. Optimum local palliation lies in matching the extent of laser induced necrosis with tumour volume. In addition, the surgical literature for hepatic resection of metastases has shown high local recurrence rates are associated with a tumour free resection margin of less than 1 to 2 cm. By the same token, it is important to identify a tumour free 'sonographic' margin around a metastasis which needs to be incorporated into the treatment zone to achieve adequate local control and increase the chances of cure in selected cases. A study of patients destined for hepatic resection whose tumours are measured accurately pre-operatively using US and CT which is then correlated with the macroscopic and microscopic limits of tumours in the operative specimen could offer useful information.

More precise tumour imaging using 3 dimensional reconstruction of CT or MR images may help delineate the exact tumour limits. Improved dosimetry or using a higher number of fibres (8 or 12) would allow complete treatment of larger tumours with increased confidence, minimal fibre manipulation and acceptable cumulative treatment times. Improved precision of needle placement and separation for small relatively inaccessible metastases is more likely to be achieved using CT guidance. This is a realistic proposition given a new generation of portable multiport semi conductor lasers currently under development which can be used in existing CT and MR suites with no modification. Real time CT monitoring could allow immediate identification of untreated contrast enhancing tumour enabling immediate treatment of residual viable tumour. This may reduce

the number of treatments per tumour allowing reliable complete tumour necrosis to be achieved after a single treatment. The disadvantage would be a heavy commitment on already over burdened CT facilities and possibly high cumulative radiation doses. Invasive probes monitoring changes in blood flow, temperature or light transmission may have a complimentary role to US, CT and MRI. A more detailed real time assessment of the influence of laser treatment would allow appropriate adjustments in laser parameters or fibre position. Recently, work on MR imaging of laser tissue interaction has been reported. Distinguishing between regenerating liver and tumour recurrence around margins previously treated may be facilitated by this technique. In addition, real time MR images with temperature sensitive sequences could lead to better prediction of the extent of tissue necrosis.

The correlation between real time US images of the extent of necrosis in normal animal liver and the true extent of necrosis at post mortem have been established. There has been no similar study confirming whether similar real time changes seen in this study truly represents the extent of tumour necrosis. Certain considerations on a theoretical basis suggest that this should not be the case. The far infra red wavelength of Nd:YAG light (1064 nm) is poorly absorbed but highly scattered predominantly in pigmented tissue such as the liver. Only light that is absorbed primarily or following scattering produce a biological effect. Unlike the normal liver, metastases are in general non-pigmented and are considered to be relatively avascular. This combination of features favour light transmission which produces no biological effect. It is necessary to assess whether this is a theoretical or a real consideration. Current animal licence regulations do not permit large animal tumour models which in any case do not exist. small animal tumour models are impractical. An alternative is to treat patients destined for hepatic resection prior to surgery. A correlation between the real time US assessment, post-treatment CT and the true extent of necrosis in the operative specimen could be established. However, there are several objections to this approach. It is probably unethical to subject a patient to a potentially hazardous treatment from which there is no discernible benefit to the individual. Secondly, the theoretical risk of needle tract seeding, propagating tumour cells into the circulation and disturbing the host tumour balance may convert a potentially curable case into an incurable

one. A useful compromise would be a study correlating the extent of real time US changes in treated tumours with the extent of necrosis on dynamic CT 24 hours from treatment. Using CT imaging as a gold standard can be justified to a certain extent on the basis of Takayasu and his colleagues study (1984). This showed good correlation between CT dimensions of tumour necrosis following chemo-embolisation with the pathological extent of necrosis in the resected specimen.

ILH is in its infancy and further research is necessary before it can be regarded as an established treatment. What is the possible future role of ILH in the treatment of hepatic metastases ? The first line treatment for patients with a limited number of discrete metastases should be hepatic resection. This study has shown that ILH can be applied percutaneously, is a relatively simple technique to perform and is well tolerated by patients. The technique is relatively safe, producing radiological evidence of tumour necrosis although, for the moment, it has to be acknowledged its influence on patient survival is unclear. However, given its simplicity, then patients unsuitable for surgery on grounds of unfitness or tumour inoperability, who might otherwise receive no treatment should be considered for therapy. Lesions which are inoperable due to the close proximity of major vessels can be treated with relative safety by ILH as rapid blood flow within such vessels confer some protection to the vessel. It is possible that following interstitial treatment, inoperable lesions may become operable as tumour necrosis and resorption allow a surgical plane to become defined. However, the major biliary radicles are sensitive to thermal insult and inflammatory strictures may develop. In the absence of effective adjuvant therapy, any form of local treatment for hepatic tumours fails to deal with the systemic nature of this disease. However, in those patients with truly localised hepatic disease and where the extent of laser mediated necrosis can be matched accurately to the extent of the tumour, the prospect for cure exists.

Alternative interstitial techniques producing local tumour necrosis in the liver such as cryotherapy, alcohol injection, and interstitial radiotherapy have their proponents and are currently the focus of active research. To put ILH in context, these techniques need to be considered in a little more detail. The merits and disadvantages of each are discussed below in the light of current knowledge. It may be possible to form some impression for which is

the best technique although clearly in the absence of a controlled trial such an assessment may be inappropriate.

6.5.1 CRYOTHERAPY

Cryotherapy, the application of a cooling agent to biological tissue to induce necrosis has been reported sporadically since the middle of the last century although advances have been hampered by technical problems (Hass & Taylor., 1948, Lemariety & Muler., 1960, Rowbotham et al., 1960). Improvements in probe design and imaging technology now allow superficial and deeply seated lesions within the liver to be treated with real time intra-operative ultrasound monitoring. The developing freezing areas can be seen as a hyperechogenic zone generated around the cryoprobe with clear demarcation from untreated liver. There is good correlation between evolving and final extent of the frozen area as seen sonographically, and the pathological margins of the extent of the necrosis produced (Gilbert et al., 1985).

Several factors operate when a cryogenic stimulus is applied to biological tissue. These include cellular dehydration, denaturing of structural and functional proteins leading to irreversible cell death. A more remote effect has been reported experimentally; namely the induction of an immunological response to residual viable tumour (Jacob et al., 1984). This is thought to the result of liberating tumour specific antigens which provoke a host immune reaction. For the moment, it is not clear whether this phenomenon has any clinical significance.

Zhou et al reported on 27 out of 60 patients with primary hepatocellular carcinoma treated with cryotherapy alone (Zhou et al., 1988). Twenty one cases out of the 60 had lesions smaller than 5 cm but what proportion of these made up the cryotherapy only treatment group is not disclosed. Patients were treated at laparotomy using a 3 to 5 cm diameter hollow plate probe that circulated liquid nitrogen through an insulated metal sheath with temporary occlusion of the hepatic blood supply. Assessment of treatment was made visually and by thermocouples placed around the treated lesion. There were no procedure related complications. The survival rates in the 27 cases treated were 33%, 23% and 4% at 1-year, 2-year and 5-year respectively. These results could almost certainly have been

improved upon as thermocouple and visual assessment make no consideration for depth and margin of the freezing front and therefore tumour eradication is likely to have been incomplete in at least some of these cases. Cryotherapy plus synchronous or metachronous resection of treated tumours were performed in 5 patients. Histological evaluation showed only scar tissue at previous tumour sites.

Unlike Zhou who treated superficial lesions only, Ravikumar treated 10 patients with multiple deeply located metastatic lesions within the liver using liquid nitrogen at -196 ^{o}C with 8mm and 12mm diameter interstitial probes under intra-operative ultrasound guidance (Ravikumar et al., 1987). The first 5 patients in the series underwent synchronous resection of the treated frozen area. The subsequent 5 patients were treated in a similar manner but 3 freeze cycles were used for each lesion and the treated area was left *in situ*. The largest iceball generated was 3 cm in diameter but there is no mention of the size or number of the lesions treated. Follow up ranged from 4 to 17 months (median of 7.5 months) and consisted of tumour imaging and serial assays of tumour markers. Those patients with elevated CEA and no gross residual disease following treatment produced a progressive fall in their titres over several months. Serial CT scans showed evidence of tumour necrosis and diminution in size of all treated lesions. Surprisingly, out of 6 patients who had lesions cryoablated and then resected (5 synchronously and 1 metachronously) a comment is only made in one patient to the effect that of two lesions, one showed evidence of viable tumour.

A further report on cryosurgery for metastatic liver disease has come from Nottingham (Charnley et al., 1989). Seven patients with a total of 39 metastases ranging from 0.5 cm to 6.5 cm in diameter were treated at laparotomy using liquid nitrogen with a 5mm interstitial probe under intra-operative ultrasound guidance. All patients were discharged 7 to 10 days after surgery. Follow up time ranged from 1 to 6 months. CT scanning of all treated lesions showed evidence of tumour necrosis and regression in size at 6 weeks. CEA levels fell in 3 patients and one patient with carcinoid syndrome became asymptomatic.

Undoubtedly, modern technology has allowed cryotherapy to evolve as a feasible and safe technique for treating focal hepatic tumour. The main drawback is the necessity for

a laparotomy making the technique relatively invasive; in addition, those unfit for general anaesthesia are excluded while retreatment in patients who relapse is impractical. Operation times may become unacceptably long when dealing with several lesions and vascular adhesions around previous treatment sites may make retreatment of recurrent disease hazardous.

An advantage of the surgical approach is that it is possible to mobilise the liver fully or extend the laparotomy incision allowing access to all parts of the liver. Thus relatively small tumours in any liver segment can be treated fully, a privilege not enjoyed by percutaneous techniques. In addition, intra-operative ultrasonography provides superior resolution when compared with conventional sonography. The absence of a soft tissue interface between the transducer and the liver allows small lesions (< 2 cm in diameter) which might otherwise be missed to be treated at a potentially curable stage. However, despite relatively inexpensive equipment (£5 000), treatment costs escalate due to prolonged hospitalisation and recovery times and demands on operating and medical time.

6.5.2 ALCOHOL THERAPY

The use of alcohol to destroy biological tissue is well established in medicine, for example, in coeliac ganglion blocks (Haaga et al., 1984). Shinagawa and Fujimoto independently reported their attempts at ultrasound guided percutaneous alcohol injection for intrahepatic neoplasms in the mid 1980's (Shinagawa et al., 1985, Fujimoto et al., 1986). Improvements in the resolution capability of ultrasonography coupled with the low costs, ease of handling and its ready availability has allowed alcohol injection of hepatic tumours to emerge as a feasible alternative in those whom surgery is contraindicated.

Livraghi, a keen advocate of alcohol therapy, has published his results in two series (Livraghi et al., 1986 & 1988). A total of 37 lesions less than 4.5 cm in diameter in 28 patients were treated by percutaneous alcohol injection under US control. Thirty three lesions were primary hepatocellular carcinomas, the remainder metastatic liver tumours. The number of injections per lesion ranged from 3 to 24 depending upon the initial diameter and assessment between successive injection. Assessment included fine needle biopsy (FNB) and US after every 3 injections with a maximum of 9 injections in the first 11

patients. Subsequent patients had FNB and CT scan performed after every 6 injections up to a maximum of 24 injections. On treatment completion, all patients had an US performed. There were no procedure related complications. Follow up time in the first 11 patients was a minimum of 3 months. In these patients, all lesions less than 3.0 cm in diameter became negative on FNB and showed volume reduction up to 100% on follow up US. However, lesions greater than 3.0 cm in diameter remained positive for malignant cells and showed no sonographic evidence of regression. In the subsequent 17 patients, all lesions were sonographically smaller and negative on FNB after a follow up time ranging from 6 to 27 months. Eight out of 12 lesions less than 2.0 cm in diameter were no longer detectable on US follow up. Four lesions metachronously resected showed no viable tumour on histological assessment. Shiina et al (1987) achieved similar results in 14 patients with single hepatocellular lesions under 5 cm in diameter treated by alcohol injection alone. The only complication was an intraperitoneal bleed in one patient 2 days after injection which settled on conservative management.

Tumour margin delineation following multiple alcohol injections is difficult due to increased tumour echogenicity hampering precision of subsequent needle placement. The problem was addressed by Sheu and his colleagues (1987) using a needle with multiple side holes so injecting several sites in known juxtaposition. One or more small steel coils were implanted before treatment to serve as landmark. Six patients with solitary HCC less than 3 cm in diameter were treated with this technique. Angiographic follow up demonstrated complete loss of tumour blush in 4 and FNB showed no viable tumour in 5 patients. Equivocally viable tumour was seen in one patient following metachronous resection of a treated lesion. These results are impressive, but judging by Livraghi's results, small tumours (< 3cm diameter) do equally well after alcohol injection without steel coil insertion. The real issue is whether steel coil can improve results when treating larger lesions.

Undoubtedly, percutaneous alcohol injection is an effective palliative and in some cases curative treatment for small hepatic tumours although the optimum volume, frequency and site of injection has yet to be determined. In Livraghi and Sheu's series, the average

volume of alcohol administered varied significantly for metastases less than or equal to 3 cm in diameter.

1) Livraghi 1986 - 5 - 10 ml per lesion.

2) Livraghi 1988 - 7 - 30 ml per lesion.

3) Sheu 1987 - 99 ml per lesion

The volume of a tumour with a diameter of 3 cm, if assumed to be spherical, is only 17 ml. In theory, injection of alcohol volumes exceeding tumour volume may be attractive as it promotes diffusion to surrounding normal liver where tumour nodules may reside. However, it is also likely that already necrotic areas are further exposed to alcohol; whether this is deleterious or not is as yet unclear. More importantly, alcohol volumes injected less than the tumour volume probably leave viable areas of tumour untreated. What is the ideal alcohol volume which should be injected in relation to tumour extent under treatment ? Based on a simple volume relationship, and assuming homogeneous alcohol distribution throughout the tumour, then the volume of alcohol injected should at least equal the tumour volume. However, experimental work has shown that alcohol passes along planes of least resistance bypassing areas of fibrous consistency which may be present from the outset or develop following initial alcohol injection. Its distribution is therefore inhomogeneous and the biological effect becomes imprecise and unpredictable (Van Eyken et al., 1991). As a consequence, the ideal volume of alcohol injected, frequency and optimum distribution of injection sites is to a large extent empirical. A second factor contributing to treatment imprecision is that while alcohol may be seen sonographically diffusing through the tumour in real time, the all important biological effect only becomes apparent several minutes to several days after injection. Good results following injection of small tumours suggest these factors are not crucial but are likely to be more significant when treating large tumours.

Attempts to overcome the problem of localising untreated areas of tumour following several alcohol injections by implanting steel coils at the injection sites has as yet to be proven for larger tumours (diameter $\geq$ 3.0 cm). As an alternative, Gelfoam has been used as a treatment marker appearing sonographically as a hyperechoeic shadow (Shiina et al., 1989). Unfortunately this appearance only persists for about 2 weeks. Hirano and his

colleagues (1989) reported that CT imaging of necrotic tumour areas was more accurate following injection of a mixture of lipiodol and alcohol. Other problems of alcohol therapy include its passage into nearby venous channels, which must be noted and due allowance made. Large injection volumes are associated with severe pain and is probably due to retrograde flow of alcohol along the needle tract with extravasation into the peritoneal cavity. This maybe controlled by limiting the the volume of alcohol injected at any one site.

The case for the use of alcohol injection is a strong one. Its advantages are many including minimal demand on manpower and equipment. The results for small tumours are promising. For example, in Livraghi series (1988), a survival rate of 92% after the first year in 12 patients treated with alcohol injections compares favourably with the results of resectional surgery for HCC less than 5 cm in diameter. In three surgical series of 28, 62 & 19 patients with HCC, Shinagawa et al (1984), Lee et al (1986) and Kinami et al (1984) reported an operative mortality of 10%, 6% and 12% with one year survival rates of 78%, 86% and 80% respectively.

The results in Livraghi's series show that in selected patients, alcohol therapy has the potential to cure and achieve short term survival rates superior to resectional surgery at a lower mortality and morbidity. Larger lesions may of course be treated with worthwhile regression but complete ablation with current techniques is unlikely.

6.5.3 INTERSTITIAL RADIOTHERAPY

Conventional external beam radiotherapy has little to recommend it for palliation of discrete hepatic metastases. The radiosensitivity of normal hepatic parenchyma compared to most metastases places a limitation on the dose that can be applied safely to the liver. While too low for cure, doses much above 30 to 40 Gy result in a significant incidence of radiation hepatitis, hepatic necrosis and biliary fibrosis (Gunderson et al., 1983). In an attempt to overcome this problem, the technique of interstitial radiotherapy has been developed allowing much higher doses to be delivered locally to the tumour with little effect on the normal surrounding parenchyma .

Nauta et al (1987) treated 12 patients with inoperable metastatic disease of the liver at laparotomy using an interstitial Iridium 192 source. The lesions were located on the

surface of the liver and their numbers varied from 1 to 11. The length of the procedure varied from 3 to 7.5 hours. Of 10 patients with raised CEA prior to treatment, 6 showed a fall within 2.5 months of treatment. CT evaluation at 1 week showed a halo of radioedema around the treated nodules.

The invasive nature of open interstitial radiation coupled with long operating times mitigate against the widespread appeal of this approach. However, Dritschilo and his colleagues (1986) treated 6 patients with hepatic metastases from colorectal carcinoma using a high intensity Iridium 192 source placed percutaneously within the tumour under US control. A total of 11 procedures were performed on tumours ranging from 2.0 to 9.5 cm in diameter. The first 3 patients in the series received a boost of external radiation. Follow up at 1 month showed 25% regression in one patient on US while CT evaluation in the remainder showed non progressive disease. All that can be said from these early results is that the technique is feasible; the follow up is too short to comment on efficacy.

Interstitial radiotherapy is a biologically attractive treatment concept. However, at present there remain several reservations. There seems to be little experimental data correlating interstitial radiation dosages with the nature and extent of the biological effect in either normal or tumour tissue. Similarly, the mechanism and time scale of healing has not been elucidated. This can be rectified but other problems remain. It is not possible to monitor the treatment response in real time and interpretation of changes seen on follow up CT imaging has not been fully studied. Further detailed work is necessary to determine the efficacy and safety of this approach before its true role can be identified.

Which interstitial technique emerges as the best (Table 6.08) ? Interstitial radiotherapy has as yet to be fully evaluated and therefore a question mark must remain over its role. Cryotherapy is an effective and safe technique but is also the most invasive of the interstitial modalities. Patients not fit for a general anaesthetic or laparotomy are excluded and treatment of those who relapse is impractical. The technique is relatively demanding of nursing and medical manpower due in part to relatively long hospitalisation times. The necessary equipment is relatively cheap compared with the price of a suitable laser but has fewer non hepatic applications.

Alcohol therapy has many factors in its favour, but there are limitations. At present, tumours 3 cm or less in diameter can be treated with a high chance of complete eradication, although larger lesions can be treated with effective control of tumour growth. This is due in part to inhomogeneous alcohol distribution leading to unpredictable and imprecise areas of necrosis. In addition, real time monitoring of the ensuing biological effect is not possible. Patients have to undergo multiple treatment sessions, be it on a day case basis.

ILH is the most effective of the thermal techniques. Predictable well defined areas of necrosis which heal safely have been demonstrated in experimental studies. It is minimally invasive procedure which is well tolerated producing radiological and in some instances, histological evidence of tumour necrosis. On theoretical grounds, there is no limit to the number of fibres that can be inserted into the liver which is a limiting factor to the extent of necrosis produced. As yet, there is no experimental data on the fate of areas of necrosis in the liver greater than 3.5 cm in diameter. In addition, further research into dosimetry may reduce the number of treatment sessions currently necessary. As with all percutaneous techniques, not all parts of the liver are readily accessible to treatment. The relative precision and predictability of ILH compared to alcohol therapy is important, yet the simplicity, ready availability and cheapness of alcohol cannot be under estimated. The significant capital cost of purchasing a suitable laser can be justified to a certain extent by its many non-hepatic applications. However, for the moment, ILH is likely to be restricted to a few specialists centres with particular expertise in medical laser application.

It is interesting to speculate on whether the favourable results of alcohol therapy for hepato-cellular carcinoma can be reproduced for metastases of equivalent size. The softer consistency of hepatomas might favour alcohol diffusion compared to the more scirrhous nature of secondary tumour where laser therapy may be more appropriate. A trial comparing alcohol therapy in both groups would be useful in allowing a more rational selection of one or either tumour for the more appropriate therapy.

It may be argued that the impact of interstitial techniques will be limited as the number of suitable patients for treatment is small in relation to the total number of patients with liver cancer. However, it may be possible to identify further patients with increased use of hepatic intra-operative US monitoring at the time of resection of primary intra-

abdominal cancers. Similarly, aggressive screening of patients at high risk of developing or harbouring asymptomatic focal hepatic tumours, for example, cirrhotic patients may yield further suitable patients.

The field of interstitial therapy is a constantly moving one. Undoubtedly advances in current treatment and follow up techniques will occur allowing larger lesions to be treated with greater confidence and precision, less cost and easier follow up. Current knowledge and development is such that treatment should now be considered for those patients with limited focal hepatic tumours which might otherwise have been left alone. Ultimately interstitial techniques may rival and improve upon the results of surgery with a lower morbidity and negligible mortality for suitably chosen patients.

TABLE 6.08. Relative merits of each interstitial technique for liver cancer.

CRITERION	*INTERSTITIAL LASER HYPERTHERMIA*	*CRYOTHERAPY*	*ALCOHOL INJECTION*	*INTERSTITIAL RADIOTHERAPY*
Ease of application	* * * *	*	* * * *	* *
Precision & prediction of effect	* * * *	* * * *	* * *	* * *
Ease of real time monitoring	* * * *	* * * *	* *	*Not Possible*
Liver accessibility	* * * *	* * * * *	* * * *	* * * *
Treatment frequency	* * *	* * * *	* *	*Unknown*
Ease of retreatment	* * * *	*	* * * *	* * *
Equipment expense	*	* * *	* * * * *	* * *
In-Patient time	* * * *	*	* * * *	* * * *
Manpower required	* * * *	* *	* * * *	* * *

*The greater the number of * the greater the relative advantage (Maximum of 5)*

CHAPTER 7. INTERSTITIAL LASER HYPERTHERMIA FOR PANCREATIC CANCER.

The work presented in this chapter includes a critical review of current ideas and controversies in the management of pancreatic cancer. In addition, the efficacy and pitfalls of techniques employed to control local tumour growth are highlighted. The rationale, method, radiological and histological features following treatment of patients with inoperable carcinoma of the pancreas using ILH are described. The possible future role of ILH in the treatment of this condition is also discussed.

7.1 INTRODUCTION

The incidence of carcinoma of the pancreas has increased over the last 50 years and accounts for 6,000 deaths per annum in the U.K (Leuin., 1981). Despite advances in imaging, anaesthetic, surgical and post operative care, the prognosis remains poor with 90% of all patients having incurable disease at the time of presentation or surgical exploration (Mossa and Leven., 1981). The 5 year survival rate is less than 5% with 85% of patients dying within 12 months of presentation. Two factors contribute to the poor outlook. Presentation occurs relatively late in the natural history of the disease so that tumours are locally advanced or are associated with distant metastases (70% of patients develop hepatic metastases). Secondly, the sensitivity and specificity of diagnostic tests are least accurate for small (1-2 cm in diameter) potentially resectable tumours. Although several possible associations including diabetes mellitus, gall stones, smoking, dietary fats and animal proteins appear to be important, as yet, it is not possible to identify a high risk group. Current serological markers are too insensitive to be of any use. Even if the perfect marker was to be identified, the dilemma would be developing an imaging technique sufficiently sensitive to locate a small asymptomatic tumour. Endoscopic ultrasound may be such a technique capable of detecting lesions less than 2 mm in diameter (Yusuda et al., 1988)

There are several limitations concerning the current treatment of pancreatic cancer. Surgical resection is the only hope of cure but is only possible in 5-10% of patients

(Connolly et al., 1987). Some debate surrounds the benefits of total pancreatectomy versus pancreato-duodenectomy for tumours in the pancreatic head. The former operation has its advocates because of concern over involved resection margins, multicentric tumours, wider lymhadenectomy and avoiding a potentially hazardous pancreatico-jejunal anastomosis. The long term survival for both operations are comparable (2-4% 5 year survival) yet the operative mortality following complete removal of the gland is 12% compared to 4% for excision of the head (Van Heerden., 1984). Thus few surgeons favour routine removal of the whole of the gland.

Disappointing survival figures following apparently curative surgery has prompted research for possible added benefits. Hiroaka et al (1984) used 3000 Gray intra-operatively following resection and noted a marked improvement in one year survival (75% versus 50%). However, no difference was noted at two years. A controlled prospective trial of resection, adjuvant intra-operative radiotherapy (IORT) plus external beam radiotherapy (EBRT) versus resection plus EBRT showed lower local recurrence rates in the IORT group (Sindellar & Kinsella., 1986). However, this did not translate into improved survival. A second prospective controlled trial of EBRT plus weekly intravenous Fluorouracil after potentially curative resection demonstrated a statistically longer median survival (21 months) for the treatment versus the control group (11 months) (Kalser & Ellenberb., 1985). These findings suggest that adjuvant radiotherapy with Fluorouracil may confer additional benefits following resection.

Partial or complete resection of the gland is associated with a significant mortality (4-10%) and morbidity and yields only an improvement in short term survival reported in a recent series at 15 months (Trede., 1987). The majority of patients relapse following resectional surgery due to recurrent lymph node/local disease and/or haematogenous metastases. Poor survival, significant early morbidity and appreciable expenditure has led some to advocate abandoning resectional surgery. Indeed, for most patients, all that can be offered is palliation for the complications of pancreatic cancer.

Current palliative tecniques for pancreatic cancer will now be considered in a little more detail.

I) COMMON BILE DUCT OBSTRUCTION

Relief of biliary obstruction can be performed surgically, endoscopically or percutaneously under radiological control. The optimum technique is hotly favoured by its proponents. The generally reported higher procedure mortality of surgical bypass (up to 20% versus 0-6%) has to be balanced against repeated hospitalisation for blocked stents and ascending cholangitis following endoscopic and percutaneous drainage (Huibregtse et al., 1986, Wong et al., 1984, Siegel & Snady., 1986, Sarr & Cameron., 1982). A prospective controlled trial of surgical versus biliary stenting showed no difference in cumulative hospitalisation time or median survival (Bornman et al., 1986). A randomized trial showed that the endoscopic method has the higher rate for relief of jaundice (81% versus 61%) with a lower 30 day mortality (15% versus 33%) compared to the percutaneous technique (Speer et al., 1987).

In the presence of liver metastases, ascites or tumour in the portal region making surgical bypass hazardous, then endoscopic stenting is preferable. For patients with non-metastatic unresectable disease with a higher probability of longer survival, then surgical drainage is preferable. The best form of surgical drainage of the biliary tree is controversial. In a review of 60 published series looking at palliation of pancreatic cancer, Sarr and Cameron (1982) concluded that choledocho-jejunostomy is preferable to cholecysto-jejunostomy as jaundice and cholangitis did not seem to occur with the former yet the operative mortality for both operations is comparable (20% versus 16%). Division of the common bile duct with an end to end anastomosis reduces the opportunity for reobstruction due tumour extension up the bile duct.

II) DUODENAL OBSTRUCTION

Whether all patients should have a prophylactic gastro-jejunostomy at the time of biliary bypass is a difficult question to answer. Duodenal obstruction occurs in between 10-20% of patients with pancreatic tumours during the course of their disease. The addition of a gastro-jejunostomy at the time of biliary bypass does not increase the operative mortality, however, relatively few patients require a gastro-jejunostomy (Ubhi et al., 1986). In addition, a motility disorder possibly due to infiltration of the coeliac plexus is often seen in

some patients (Sarr & Cameron., 1982, Weaver et al., 1987) and may be aetiological in those with delayed gastric emptying following a gastro-jejunostomy (Schantz et al., 1984). There is also some evidence to suggest duodenal obstruction occurring some time after a biliary bypass is a terminal event and a late gastro-jejunostomy may be a futile procedure (Weaver et al., 1987, Brooks et al., 1981)

III) PAIN

Abdominal and back pain maybe the most distressing symptom for the patient with incurable pancreatic cancer. As will be discussed later, IORT has been reasonably effective in controlling this. A study at the Massachusetts General Hospital noted that 50% of patients were totally pain free within 1 week of IORT with an additional 25% reporting significant improvement (Swanson et al., 1988, Shipley et al., 1984a).

Chemical splanchnicectomy of the coeliac plexus either performed intra-operatively or percutaneously using phenol or alcohol is the commonest approach for pain relief. Up to 90% of patients experience relief which can last for between 2 to 4 months (Flanigan & Kraft., 1978, Leung et al., 1983).

IV) METASTASES FROM PANCREATIC CANCER

For the patient with metastatic disease, no single or combination of chemotherapeutic agents has been shown to be effective (O'Connell., 1985, Bukowski et al., 1983, Gastrointestinal Tumour Study Group., 1985 & 1986). Alternative experimental techniques such as radiofrequency hyperthermia (Falk et al., 1986), antioestrogen therapy (Tonnesen & Kamp-Jensen., 1986, Crowson et al., 1986) and immunotherapy (Sindelar et al., 1986) are of no proven benefit.

V) CONTROL OF LOCALISED UNRESECTABLE PANCREATIC CANCER

For most patients unsuitable for surgical resection, little attempt is made at controlling local tumour growth. Localized tumour is taken to mean apparently macroscopically contained pancreatic cancer although it is known that microscopic metastases may already exist in the vast majority of patients.

As well as producing local tumour regression, other benefits may include preventing or prolonging the interval to the onset of obstruction to nearby structures such as the duodenum, common bile duct or portal vein or alternatively prevent or relieve pain due to local neural infiltration. While accepting that most patients with pancreatic cancer die from a combination of several factors associated with advanced malignancy, it is conceivable that adequate locoregional control may allow patients the opportunity to succumb to the complications of uncontrolled distant rather than local disease.

Median survival for localized but unresectable pancreatic cancer untreated or treated with bypass only is approximately 6 months (Dunn., 1987). EBRT (Whittington et al., 1984), neutron beam therapy (Cohen et al., 1985) and intra-luminal radiation combined with EBRT (Molt et al., 1986) do not confer any useful benefit.

EBRT combined with Fluorouracil may confer a survival advantage compared to radiation alone. In a study of 194 patients, Fluorouracil and EBRT (4000 or 6000 Gray) produced significantly longer survival (10 months) than EBRT alone (5.5 months). Fourty per cent of the combined therapy group were alive at 1 year compared to 10% of the EBRT group. Adriamycin is no more effective than Fluorouracil in increasing survival (Gastrointestinal Tumour Study Group., 1985)

I^{125}, EBRT & 5FU

A limiting factor to the radiotherapeutic dose that can be delivered safely to the tissue is the risk of injury to surrounding organs. One solution has been intra-operative radiotherapy allowing direct delivery of boost radiation safely to the tumour. Interstitial implants using Iodine 125 (I^{125}) or particle therapy using an electron beam from an accelerator have been employed. Several groups have investigated the potential benefits of I^{125} implantation combined with EBRT and Fluorouracil. Median survival times reported ranged from 8 to 14 months (Morrow et al., 1984, Shipley et al., 1984b, Niser-Syed et al., 1983). The largest reported experience using this method comes from the Thomas Jefferson University Hospital where 54 patients were treated (Mohiuddin et al., 1986). Median survival was 14 months with an operative mortality rate of 7.4% and a morbidity rate of 52%. Complications arose from a combination of multiple needle placement into the

pancreas and high dose EBRT leading to bleeding, pancreatitis and fistulae. The complications of this technique make it less attractive than electron beam IORT.

IORT, EBRT & 5FU

Several centres have used this combination predominantely for unresectable pancreatic cancer. Abe (1985) reported his results of treatment of advanced pancreatic carcinoma. Three treatment regimens were used: 1) surgery alone, 2) surgery plus intra-operative radiotherapy, 3) surgery, IORT and EBRT. In each group, roughly 50% had liver metastases and 80% underwent bypass only, while 20% had incomplete resections. Results are summarised in Table 7.01. Patients without liver metastases had significantly longer median survival when treated with surgery, IORT and EBRT compared to surgery or surgery and IORT. This would seem logical as there is no reason for IORT to improve survival in patients with metastatic disease. However, it should be noted that published reports (Mohiuddin et al., 1986) show equivalent median survival to that obtained with surgery, IORT and EBRT with EBRT ± chemotherapy. The Mayo clinic compared bypass surgery, IORT plus EBRT versus bypass surgery and EBRT alone for locally advanced unresectable pancreatic cancer (Gunderson et al., 1987). Median survival was (Table 7.01) was the same in both groups but local control was significantly higher with IORT (65% versus 19% at 2 years)

Although a median survival of 12 months with excellent local control in 93% of patients was achieved in Gunderson's series, long term survival was not improved significantly because most patients died from distant disease. The National Cancer Institute (Sindellar & Kinsella., 1986) reported a randomized controlled study comparing IORT, EBRT and 5-Fluorouracil versus EBRT and 5-Fluorouracil. Median survival (8 months) and time interval to disease progression were superior with the IORT group. The largest experience with the longest follow up of IORT, EBRT and 5FU for localised unresectable disease comes from Massachusetts General Hospital. A median survival of 16.5 months has been reported with local control in most patients (Tepper et al., 1987).

IORT (electron beam or interstitial I^{125}), EBRT and 5-Fluorouracil, while achieving local control in the majority of patients do not influence long term survival; most patients

dying from distant disease or peritoneal metastases. It would seem that IORT is an important component in obtaining local tumour control. However, the need for a laparotomy with its implications on morbidity, cost, hospitalisation and recovery times is undesirable given the palliative nature of IORT in a patient group with limited life expectancy. Patients unfit for general anaesthesia are excluded while treatment of patients who relapse is clearly impractical. In addition, treatment regimens are complex and IORT is not without its problems. An advantage of boost radiation using electron beam IORT versus I^{125} implantation is the absence of mortality and low morbidity with the former (Shipley et al., 1984a).

REFERENCE	*TREATMENT*	*MEDIAN SURVIVAL*
DUNN (1987)	*NONE*	*6 MONTHS*
ABE (1985)	**SURGERY*	*6 MONTHS*
	**SURGERY+IORT*	*6 MONTHS*
	**SURGERY+IORT+EBRT*	*12 MONTHS*
MOHIUDDIN ET AL. (1986)	*SURGERY+EBRT±CHEMO*	*12 MONTHS*
	SURGERY+I^{125}+EBRT+5-FU	*14 MONTHS*
SINDELLAR & KINSELLA (1986)	*SURGERY+IORT+EBRT*	*8 MONTHS*
GUNDERSON ET AL. (1987)	*SURGERY+ EBRT*	*12 MONTHS*
	SURGERY+ IORT+EBRT	*12 MONTHS*
TEPPER ET AL. (1987)	*SURGERY+IORT+EBRT+5 FU*	*16.5 MONTHS*

*Table 7.01 - Median survival in patients with pancreatic cancer following various treatment regimens. All surgery is bypass unless denoted by * = bypass or incomplete resection.*

However, a major late complication is gastrointestinal bleeding (10%) and duodenal obstruction (Swanson et al., 1988, Shipley et al., 1984a). The incidence of both

complications can be reduced by minimizing the amount of duodenum in the IORT field and performing a gastro-jejunostomy at the time of IORT.

From this review, it is apparent that achieving optimum palliation depends on two factors. The first is to develop a simple and safe minimally invasive technique effective at controlling local tumour growth with the capacity to retreat easily in the event of local relapse. In principle, Interstitial Laser Hyperthermia (ILH) has the potential to fulfil such a role. It can be applied percutaneously to almost any solid viscus within the peritoneal cavity using US guidance. In theory, locally recurrent disease can be treated as often as is necessary. Given that survival is limited by distant disease which is clearly beyond the confines of any form of regional treatment, then an effective chemotherapeutic agent needs to be developed. Ultimately, a combined thermochemotherapeutic approach may be developed providing effective local and distant tumour control simply and at a low morbidity and negligible mortality.

It is with these thoughts in mind that the work presented in this section was carried to assess the efficacy and safety of ILH for inducing necrosis in pancreatic cancer. Preliminary experimental work in canine pancreas using single and multiple fibres coupled to a Nd:YAG laser has been performed by Steger and his colleagues (1987). They demonstrated precise and predictable areas of necrosis the extent of which depended upon the laser parameters used. However, the margin between predictable and safe necrosis and producing fatal organ damage was small and depended upon two factors. Treatment with a laser fibre up the pancreatic duct produced duct rupture with an ensuing fatal pancreatitis. A similar outcome occurred if laser powers in excess of 2 watts were used irrespective of fibre position. Powers of 1 watt per fibre produced safe areas of necrosis ranging from 1.7 cm in diameter with a single fibre up to 4 cm with 4 fibres in juxtaposition. Healing occurred within 1 month by fibrosis. This demonstrated that once the appropriate laser parameters and fibre position were defined, ILH can be safely applied to normal pancreas.

7.2 METHOD

Over a 30 month period, 5 patients (4 male and 1 female) with a mean age of 60 years (42-68 years) were referred to the National Medical Laser Centre, University College

Hospital for assessment and consideration for treatment using percutaneous ILH. Selection criteria for treatment were relatively flexible and included that no tumour exceed a diameter of 5 to 6 cm while being circumscribed and well defined on ultrasonography. Ultrasound (US) or computerised tomographic (CT) evidence of peripancreatic lymph node involvement was not necessarily a contraindication to treatment but the presence of hepatic metastases or ascites was.

The female patient had developed a recurrence in the pancreatic remnant following a distal pancreatectomy for an adenocarcinoma in the tail of pancreas. The remaining 4 patients had locally advanced cytologically or histologically proven malignant tumours in the head of the gland. Two patients had a previous laparotomy with surgical bypass of the biliary tree in addition to a gastro-enterostomy in one. The remaining two had an endoscopic stent; one inserted prior to laser treatment and the other following therapy. Two of the patients were deemed to have inoperable disease on conventional operative criteria. In the remaining 3 patients, surgery was felt to be inappropriate by the referring physician. Treatment options and likely outcome were discussed with all patients. The experimental nature and possible benefits of ILH were also highlighted.

The first patient in the series was treated using a single fibre delivery system coupled to a pulsed Nd:YAG laser (Lumonics MS35 LD). All other treatments were performed using a continuous wave Nd:YAG laser (Flexilase, Living Technology, Glasgow) coupled to a 1 x 4 200 micron star coupler (Canstar, North York, Ontario, Canada). This allowed simultaneous transmission of laser light of equal intensity at clinically relevant powers down 4 fibres using a single laser. The laser and laser fibres were prepared in an identical manner to that described in chapter 6. Both the pulsed and continuous wave Nd:YAG produce the same biological effect when using equivalent powers and exposure times (Matthewson et al., 1986).

Patients were carefully assessed clinically to exclude widespread metastatic disease. Baseline full blood count, clotting screen, urea and electrolytes, glucose and amylase were performed. In addition, serum was grouped and saved and a chest radiograph requested to exclude pulmonary metastases. To determine tumour site, extent, its enhancement pattern and exclude hepatic metastases an US (Aloka 650, Japan) and dynamic contrast enhanced

CT scan (Siemens, Somatom, DR) with delayed images were performed where possible. Scans were taken using contiguous 8 mm slices following both oral and intravenous bolus of non-ionic contrast in addition to delayed scans through the same area approximately 45 to 60 minutes after injection.

Patients were starved 6 hours prior to treatment. Venous access was secured using a 17 gauge intravenous cannula and the treatment performed following intravenous sedation (Diazepam 5-10 mg, Pethidine 75-100 mg). In addition, a 24 hour regimen of intravenous prophylactic antibiotics (Flucloxacillin 500 mg 6 hourly, Gentamicin 60-80 mg 8 hourly) were given. The abdominal wall was infiltrated with 10-20 ml of 1% lignocaine at the intended puncture site. Treatment monitoring consisted of sequential blood pressure, pulse rate, respiratory rate and continuous transcutaneous oxygen saturation measurement.

The tumour was visualised sonographically using a 3.5 MHz transducer (Aloka 650, Japan). One to 4 hollow 19 gauge needles (0.8 mm diameter) were inserted percutaneously into the tumour under US control. The needle tips were in juxtaposition with a separation of 1.0 to 1.5 cm to ensure treatment of all intervening tumour between fibres. A suitably prepared 200 micron from a 1 x 4 200 micron coupler was inserted down each needle so that 3 to 4 mm of bare silica core lay within the tumour. The laser which had been preset to a steady output of 1.5 to 2.0 watts per fibre was fired for 500 seconds. Subsequent fibre manipulation allowed contiguous areas of tumour to be treated so that a confluent area of necrosis could be achieved. The evolving thermal changes at the treatment sites were monitored in real time. Following treatment, patients returned to the ward and were observed closely for 24 hours. Repeat haematological and biochemical profiles were performed the next day in conjunction with a full clinical assessment. All patients were discharged within 48 to 72 hours from treatment.

The extent of laser induced necrosis was assessed by comparing the tumour enhancement pattern on pre and post-treatment CT scans. Areas of non-enhancement which previously enhanced were considered avascular and therefore non-viable as a result of laser treatment. No fixed treatment follow up protocol was adhered to as the clinical profile for each patient varied. It is therefore instructive to present a brief summary of each patient's case.

7.3 RESULTS

The smallest tumour treated was 3 cm in diameter while the largest approached 6 cm. A total of 7 treatments were carried out using an average energy per treatment of 5720 joules (1000 to 20000 joules). To a certain extent, treatment energy was tailored to tumour size although initially low energies were used reflecting a cautious approach on our part to do no harm.

Real time US monitoring showed changes similar to those seen in the treatment of hepatic metastases and described in the chapter 6. Initially, a hyperechogenic area developed around each of the laser fibres which progressively enlarged in real time. Immediately at the end of treatment, the hyperechogenic zones had merged with each other leaving a confluent hyperechogenic area the extent of which may reflect the zone of irreversible tumour damage (Figure 7.01a & b). This appearance persisted for 7 to 10 days from treatment. Within 8 weeks of treatment, areas of tumour necrosis on US appeared as well defined cystic lesions within solid tumour of mixed echogenicity (Figure 7.02a & b). Dynamic follow up CT images mirrored the sonographic features. Treated tumours appeared as sharply demarcated non-enhancing areas. By comparison, surrounding viable tumour enhanced with clear distinction between necrotic and viable tumour (Figure 7.03a & b).

CASE 1 - A 61 year old woman underwent a distal pancreatectomy and splenectomy for an adenocarcinoma in the tail of the pancreas. Eighteen months following surgery, the patient developed progressively severe upper abdominal pain. US and CT imaging revealed a 3 cm diameter recurrence in the pancreatic remnant to the right of the portal vein and overlying the inferior vena cava. This was felt to be unsuitable for further surgical intervention.

Using a single fibre delivery system, four sites within the tumour were treated (Total energy of 2650 joules). Sonographic assessment immediately at the end of treatment showed increased tumour echogenicity at the treatment sites (Figure 7.01a & b). Daily serum amylase estimations over the subsequent three days showed a small rise at 24 hours returning to the pre treatment level after 48 hours. A CT scan 14 days following treatment

showed retroperitoneal oedema and an increase in the extent of necrosis within the tumour. A concurrent US demonstrated a patent and hence undamaged inferior vena cava and portal vein. However, the patients predominant symptom of abdominal pain was unaltered by her laser treatment. Three months after treatment, repeat US of the upper abdomen revealed the tumour within the pancreatic remnant to measure 5.3 cm in diameter associated with extensive metastatic liver infiltration. The patient died three months later from extensive disseminated disease. A post mortem was not carried out.

CASE 2 - A 68 year old man presented to his general practitioner with a short history of upper abdominal pain. CT and US imaging of the upper abdomen showed a 5 by 3.5 cm mass in the neck of the pancreas extending to the head. This was associated with extensive peripancreatic node involvement. Surgery was felt to be inappropriate and the patient was referred for laser treatment.

A further US showed minimal dilatation of the intrahepatic biliary ducts and a liver function test profile was normal. Despite this, it was felt that there was a substantial risk of precipitating acute obstruction of the biliary tree due to the inevitable local oedema that would follow laser treatment of the tumour. Due to logistical problems, it was not possible to insert an endoscopic stent into the common bile duct prior to treatment. The first treatment was carried out using a single fibre delivery system (1000 joules) to be followed by a multiple fibre treatment (2400 joules) four weeks later. An ultrasound scan performed two weeks after the first treatment showed increased tumour echogenicity. Post treatment serum amylase and liver function test profiles performed 24 hours after each treatment remained within normal limits. However, seven days following the second treatment the patient developed obstructive jaundice. At ERCP, an endoscopic stent was inserted to good effect. The medial duodenal wall was noted to be intact. A CT scan performed 2 weeks following the second treatment showed several small areas of non-enhancement within the tumour compatible with laser induced tumour necrosis. These represented only a small percentage of the total volume of the tumour which now measured 5 by 4 cm and is in keeping with a low treatment energy used. Following this, the patient's condition began to deteriorate slowly and he died 6 weeks later. A limited post mortem examination revealed a

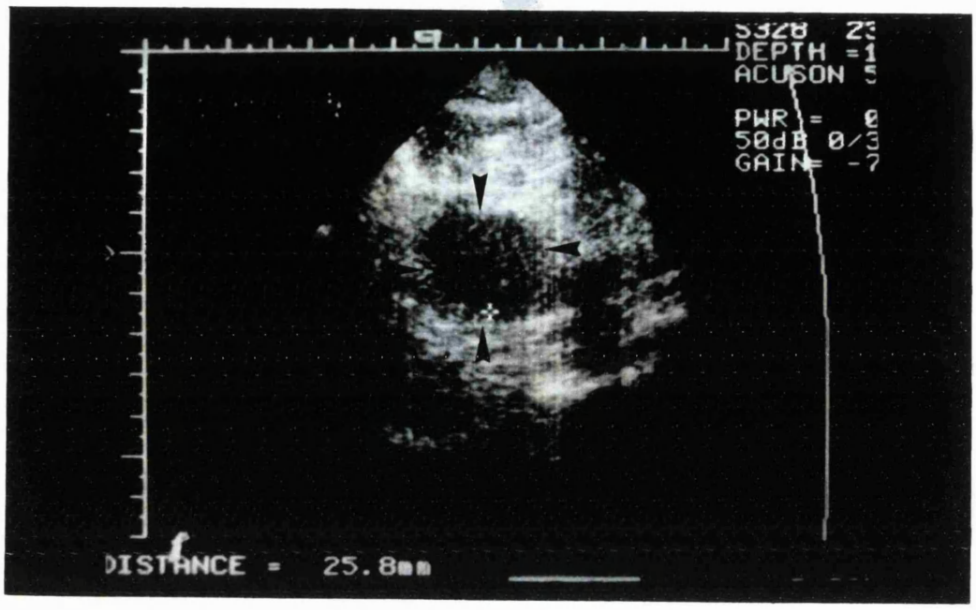


Figure 7.01a. US image of a 2.5 cm hypoechogenic recurrence (arrowed) in the pancreatic remnant following a distal pancreatectomy for adenocarcinoma.

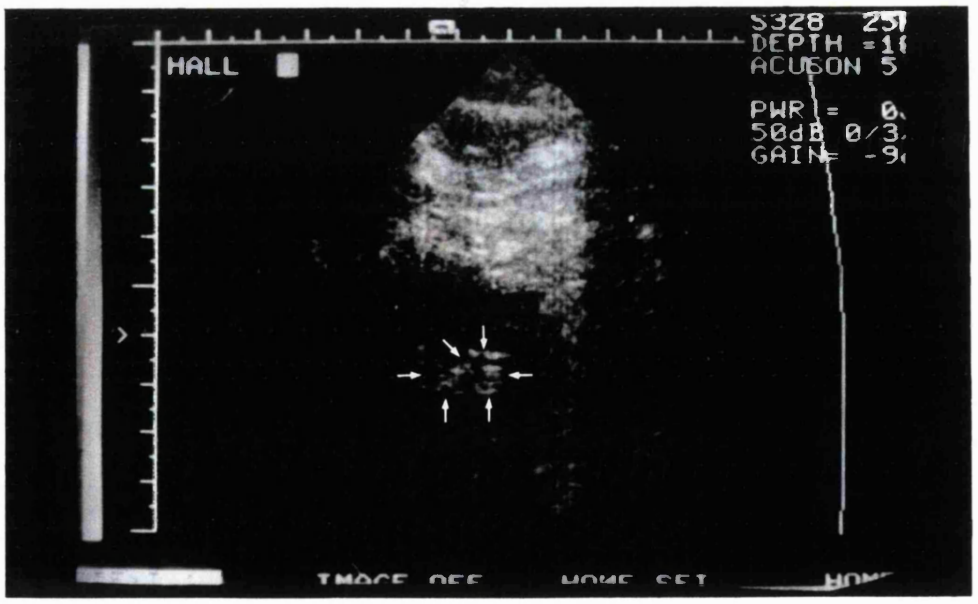


Figure 7.01b. The same lesion immediately following treatment. A hyperechogenic area (arrowed) occupying the lower third of the tumour corresponds to the treatment site.

pancreas almost completely replaced by tumour with extensive peripancreatic lymph node and hepatic metastatic disease. A marked degree of autolysis made it difficult to clearly identify any areas of laser mediated tumour necrosis on histological assessment.

CASE 3 - A 62 year old man underwent a choledocho-jejunostomy with a jejuno-jejunostomy for an inoperable carcinoma in the head of the pancreas. A follow up CT and US scan 11 months later showed a 4 to 5 cm diameter mass in the head of the pancreas invading the superior mesenteric vein and contiguous with the inferior vena cava. At this stage the patient was referred for laser treatment.

A multiple fibre laser (3 fibres) treatment was carried out uneventfully (3000 joules). The patient's post treatment amylase and liver function test profile remained within normal limits. A CT scan at 4 weeks showed three cystic areas each measuring up to one cm in diameter compatible with laser induced tumour necrosis (Figure 7.03a & b)). It is likely that each of these cystic areas represents a zone of tumour necrosis centred around each of the three laser fibre used. An US at 2 months following treatment revealed enlargement of the cystic areas reaching an average diameter of approximately 1.5 cm. These areas had begun to coalesce (Figure 7.02a & b)). These changes represented approximately 10-15% of the total tumour volume, the dimensions of which had not altered significantly over the preceding 5 months. Surprisingly, shortly after the US assessment which showed static tumour growth, the patient developed duodenal obstruction requiring a gastro-jejunostomy. This was performed at another hospital and unfortunately no comment was made on the status of the pancreas at laparotomy.

A further uneventful multiple fibre laser treatment was carried out 3 weeks following the surgery (3000 joules). Ultrasound monitoring at this stage showed that the cystic areas had all resolved. The patient was discharged home and remained well for a further 5 weeks when a slow upper gastrointestinal haemorrhage necessitated admission to the local hospital. A gastroscopy to the second part of the duodenum failed to localise the source of the bleeding. There was no evidence of laser mediated damage or tumour invasion of the medial duodenal wall. The bleeding stopped spontaneously but the patient died a few days later.

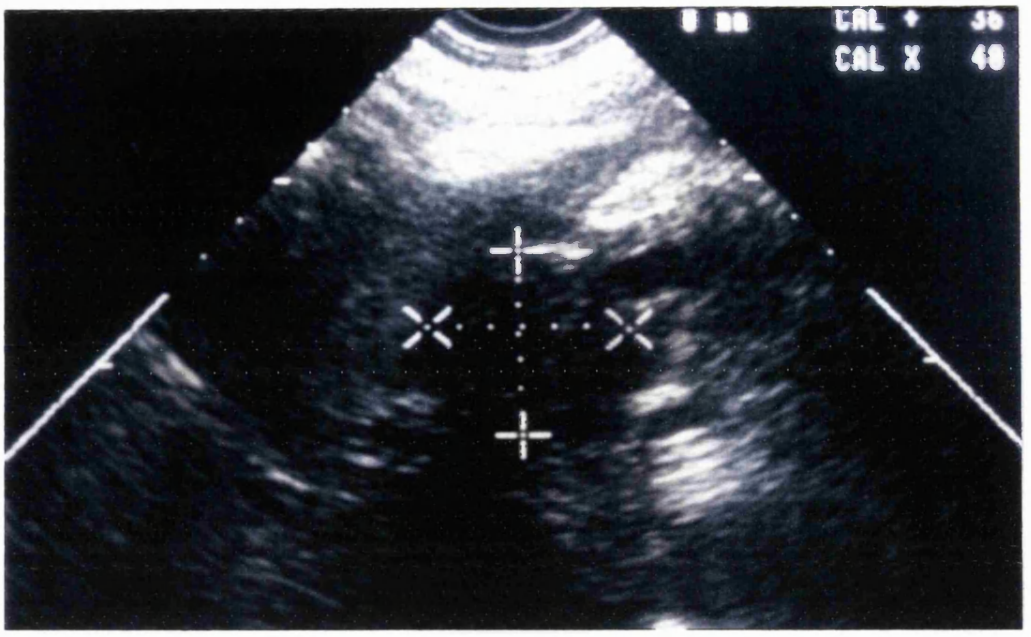


Figure 7.02a. US appearance of a 4 to 5 cm pancreatic tumour in the head of the pancreas (+.....+) & (x.....x).

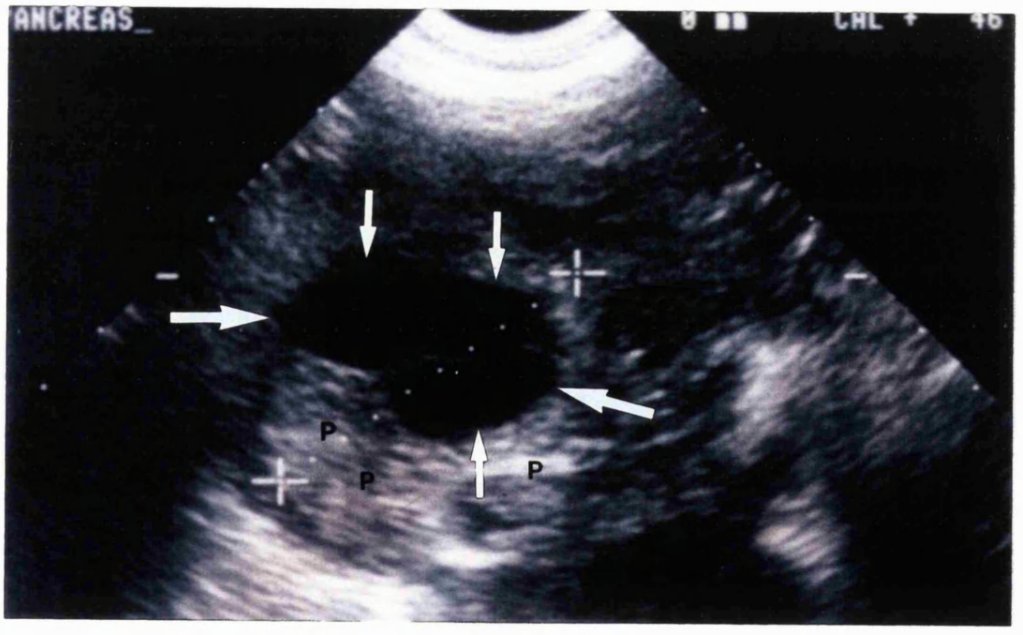


Figure 7.02b. The same tumour 8 weeks following treatment. There are three well defined cystic areas (arrowed) beginning to coalesce within the pancreatic tumour (P).

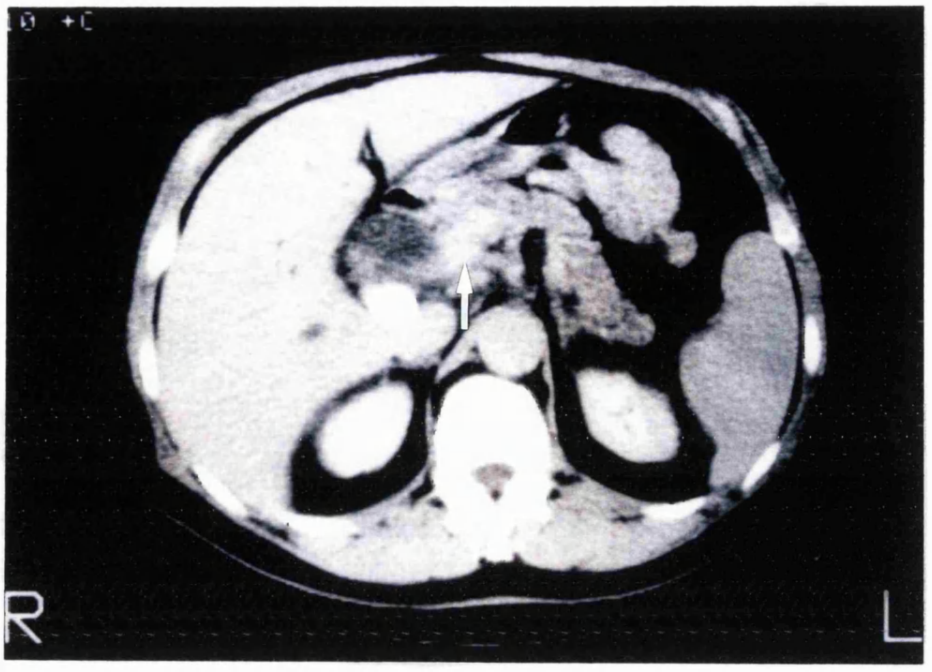


Figure 7.03a. Pre-treatment CT showing a solid mass in the pancreatic head (arrowed).

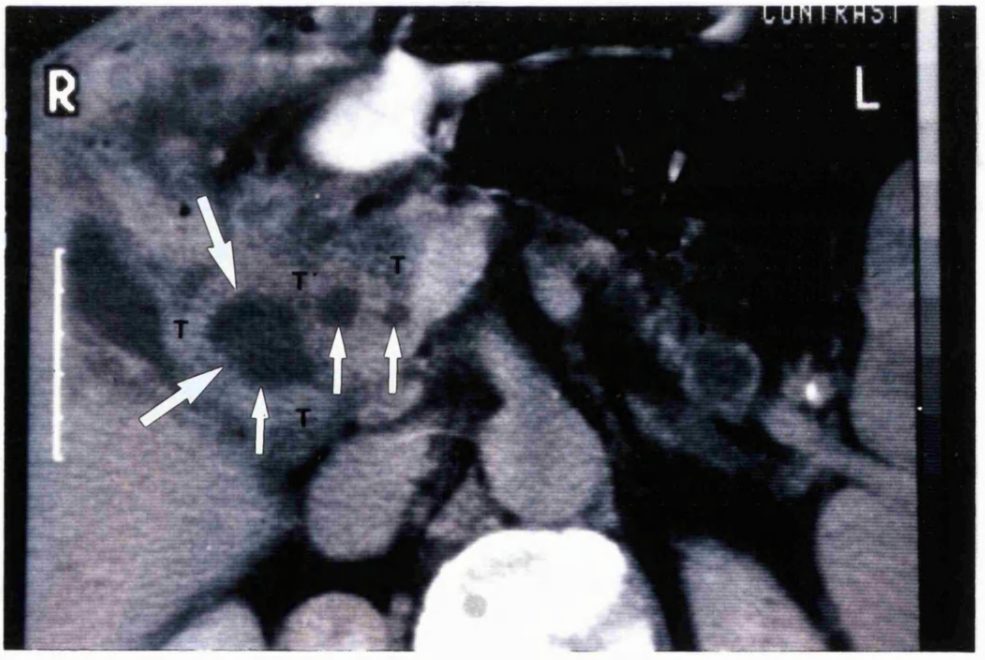


Figure 7.03b. Four weeks from treatment, a contrast enhanced CT scan reveals 3 well defined cystic areas of tumour necrosis (arrowed) corresponding to those seen in figure 7.02b. Viable pancreatic tumour (T) remains.

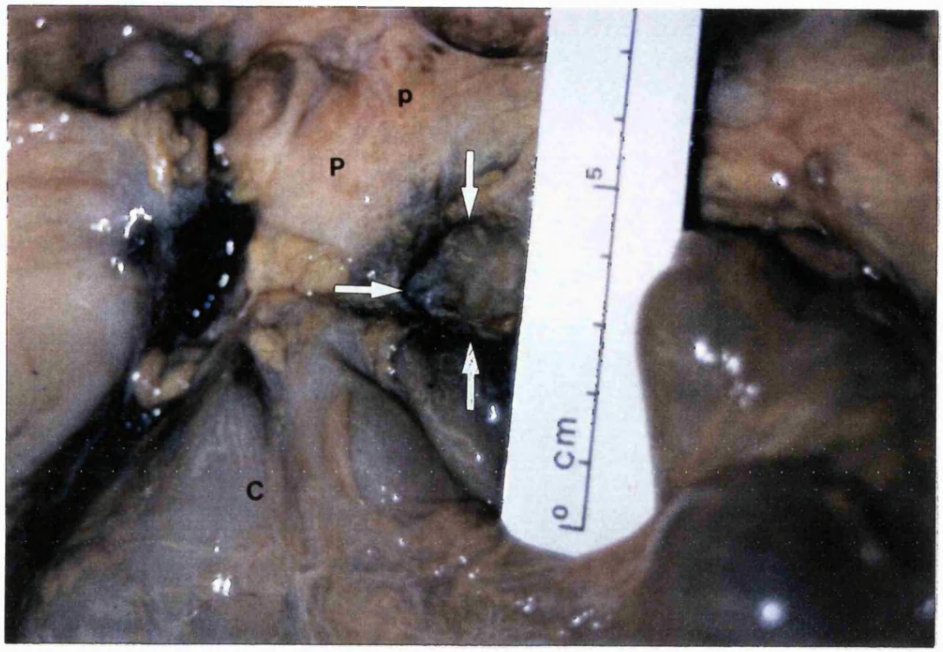


Figure 7.04. Post mortem appearance of the pancreas (p) and adjacent transverse colon (c) 6 weeks from treatment. A 2 cm well defined ulcerated area (arrowed) is present within an extensive pancreatic tumour.

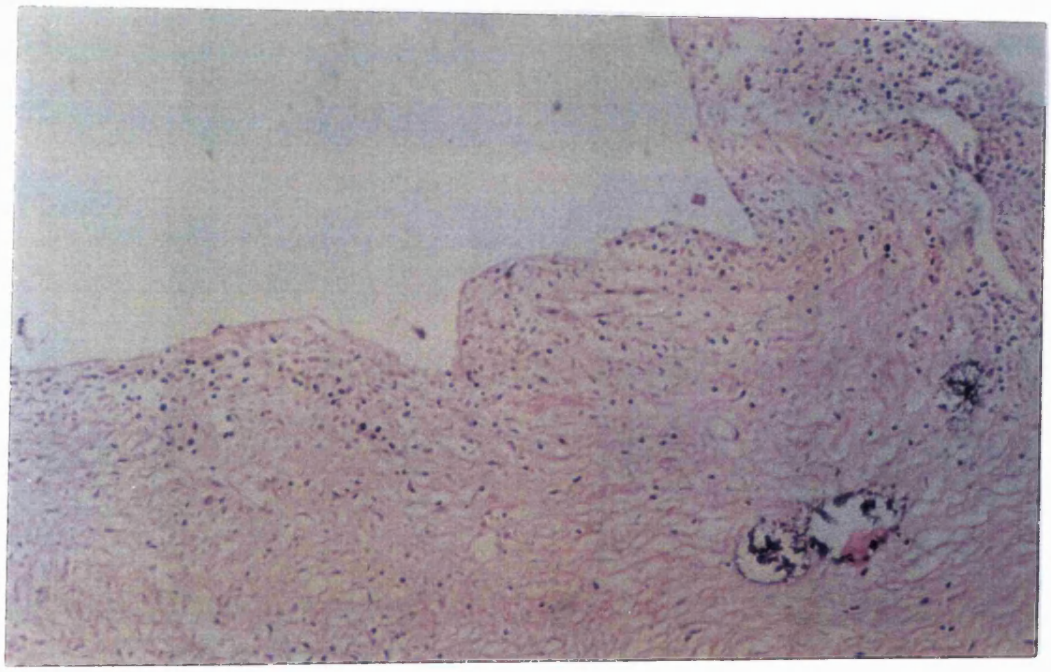


Figure 7.05. High power histological appearance of the ulcerated area noted in figure 7.04 (H & E stain). A well defined margin devoid of an epithelial lining with a surrounding chronic inflammatory cellular infiltrate is present.

A limited post mortem was performed to assess the extent and nature of the laser treatment on the pancreatic tumour. This revealed three discrete ulcerated necrotic areas measuring approximately 2 cm in diameter within an extensive pancreatic tumour at sites compatible with the last laser treatment (Figure 7.04). Examination of the second part of the duodenum failed to show any thermal damage or ulceration of the tumour. More importantly, there was no fistulation of any necrotic tumour areas into the duodenum to account for the patient's haemorrhage. Again, there was extensive metastatic intra-abdominal disease. Histological evaluation of the ulcerated areas showed a well defined cystic cavity devoid of an epithelial lining and surrounded by a chronic inflammatory cellular infiltrate (Figure 7.05). Autolysis of the pancreas made it difficult to clearly identify any viable surrounding tumour; nevertheless it is felt the cystic areas represented the legacy of the previous laser treatment.

CASE 4 - A 42 year old man living in the United States presented with abdominal pain, weight loss and steatorrhoea. There was no history of jaundice. A CT scan revealed a large mass in the body of the pancreas. Fine needle aspiration confirmed malignant cells consistent with adenocarcinoma. At laparotomy, a 6 cm mass within the pancreas extending to the ligament of Treitz and invading the superior mesenteric artery was found and judged unresectable. In addition, a biopsy positive 2.5 cm metastasis was noted in the right lobe of the liver. A cholecysto-jejunostomy and gastro-jejunostomy were fashioned and the patient subsequently treated with Leucovorin and 5-Fluorouracil.

Eighteen months following surgery, the patient presented himself for ILH treatment. A dynamic CT scan showed a 6 cm tumour arising from the head of the pancreas with infiltration of the retroperitoneum (Figure 7.06a). There were enlarged nodes in the peripancreatic area and the porta hepatis, however, there was no evidence of hepatic metastases. In view of the patient's young age, absence of detectable liver metastases and relatively long survival from diagnosis (20 months), it was felt reasonable to attempt to debulk the tumour using ILH.

The tumour was treated using a 4 fibre 200 micron canstar coupler at 5 contiguous sites using 2.0 watts per fibre applied for 500 seconds (20000 joules). Immediately

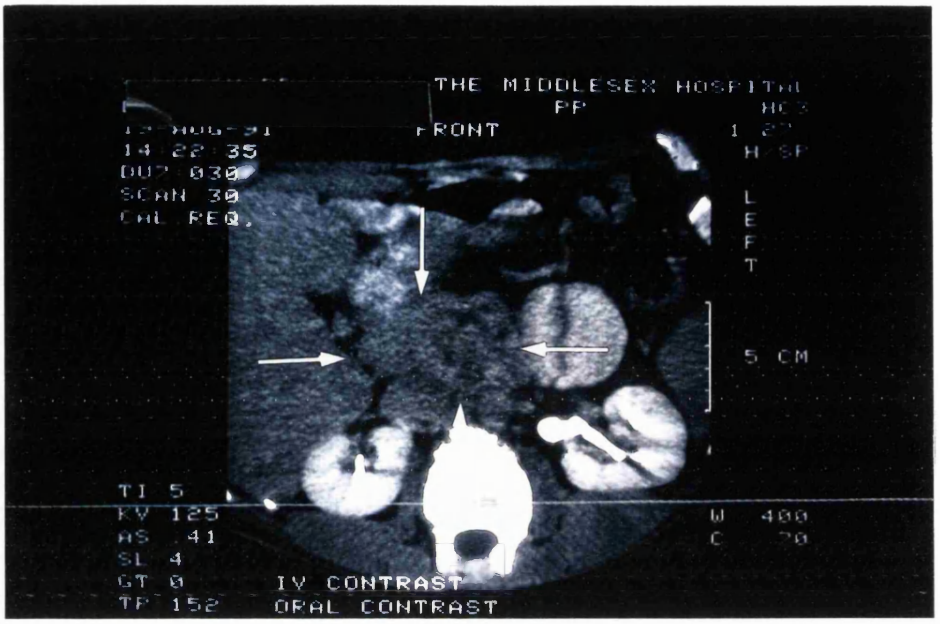


Figure 7.06a. Contrast enhanced CT showing a 6 cm mass in the head of the pancreas (arrowed) with infiltration of the retroperitoneum.

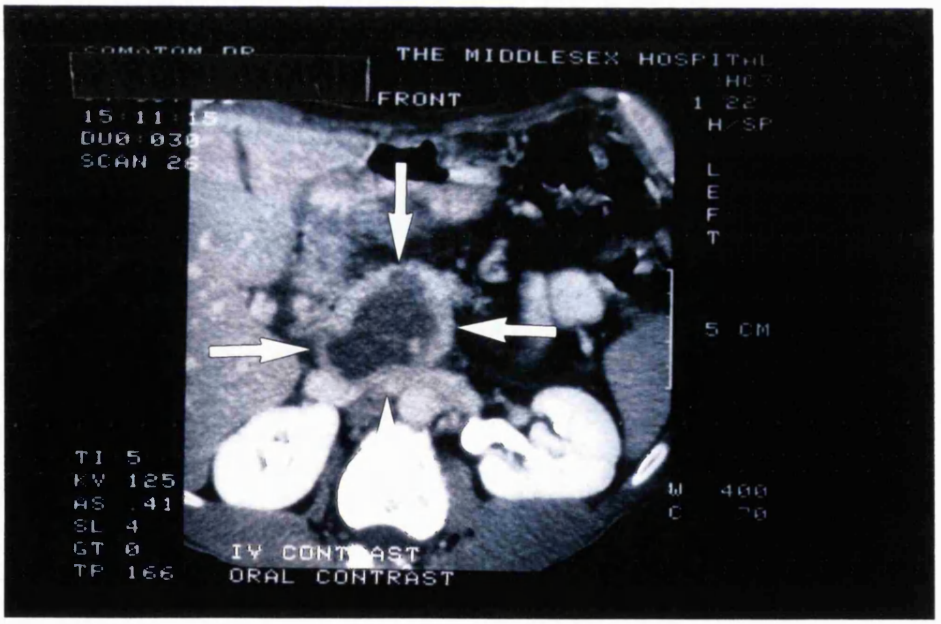


Figure 7.06b. The same tumour 24 hours after treatment following contrast enhancement. A 5 cm diameter area of non-enhancing tiumour is evident indicating successful devascularisation. A thin rim of enhancing and therefore viable tumour persists.

following the procedure, the patient complained of severe abdominal pain requiring narcotic analgesia. There were no abnormal physical signs at this stage and the patient's vital signs were normal. The pain abated within 24 hours and a subsequent serum amylase was within normal limits. A contrast CT scan at 24 hours showed a 5 x 5 x 4 cm area of non-enhancing tumour indicating successful devascularisation of a very significant volume of tumour. However, a thin rim of enhancing and thus viable tumour could be seen (Figure 7.06b). The portal vein remained patent while the coeliac axis and superior mesenteric artery opacified normally. The patient was discharged and flew back to the states 3 days after treatment.

Two weeks following treatment the patient began to pass dark red stool. Although not compromised haemodynamically, the haemoglobin fell significantly. At gastroscopy, a circumferential diffusely necrotic ulcer in the second part of the duodenum was found. There was no active bleeding. The macroscopic appearances were consistent with either tumour invasion or possibly thermally damaged duodenal wall. A biopsy showed a glandular epithelium with acute inflammation, ulceration and necrosis. No tumour tissue was identified. A repeat gastroscopy 6 weeks later showed polypoid ulceration in the duodenal bulb. It was still impossible to decide if this represented ulcerating tumour or ischaemic changes following laser therapy. Repeat biopsy showed no evidence of tumour.

The patient died 9 months following laser therapy from disseminated malignant disease. There were no further episodes of gastrointestinal bleeding.

CASE 5 - A 67 year old man with known insulin dependant diabetes mellitus presented with a 3 week history of painless obstructive jaundice associated with pruritus and dark urine. US confirmed dilated intrahepatic ducts, a dilated common bile duct and grossly distended gall bladder. In addition a 5 cm mass in the head of the pancreas was noted but no hepatic metastases. ERCP showed a dilated pancreatic and common bile duct associated with a low stricture in the later. These features were consistent with a pancreatic carcinoma. An endoprosthesis was inserted to decompress the biliary tree. A subsequent core biopsy confirmed tissue infiltrated by a pleomorphic tumour showing no gland formation; the

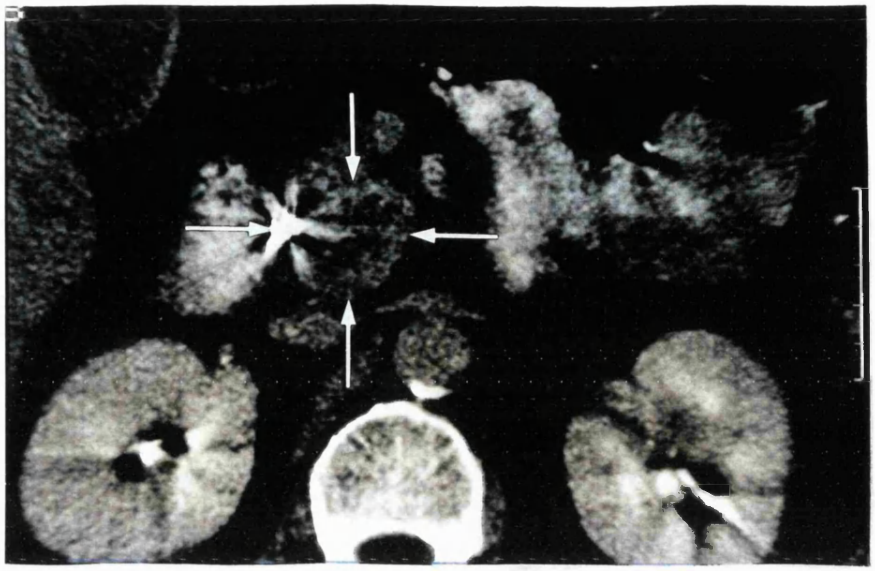


Figure 7.07a. Contrast enhanced CT showing a 5 cm mass in the head of the pancreas (arrowed).

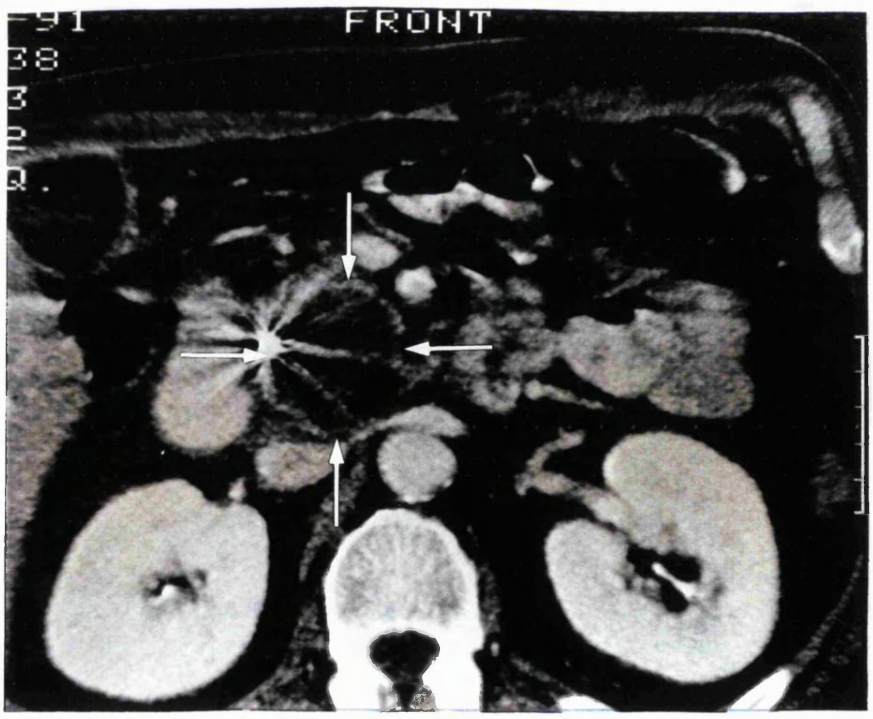


Figure 7.07b. 24 hours follow up contrast CT reveals a non-enhancing area at least 3 cm in diameter (arrowed) indicating devascularisation of a significant proportion of tumour.

appearances consistent with a poorly differentiated carcinoma. Repeat US showed progressive decompression of the biliary tree confirmed by improving liver function tests (LFT). The gall bladder remained distended suggesting low insertion of the cystic duct into the common bile duct which was occluded by tumour. Contrast enhanced CT scan showed a 4 x 3 x 3 cm mass in the head of the pancreas but no liver metastases (Figure 7.07a). The treatment options (do nothing, surgery, chemotherapy or ILH) were discussed with the patient who opted for the laser treatment.

Repeat LFT 3 weeks following stenting and just prior to laser treatment indicated a degree of cholestasis persisted despite stenting (Bilirubin 111 [3-7 μ moles/litre], Alkaline Phosphatase 629 [100-280 Iu/litre], Aspartate Transaminase 70 [11-55 Iu/litre]). The superior aspect of the tumour was treated using a 4 fibre 200 micron canstar delivery system at a power of 2.0 watts per fibre applied for 500 seconds at 2 contiguous sites (8000 joules). As per routine, the procedure was covered with 3 doses of intravenous Cefuroxime 750 mg and gentamicin 80 mg. The procedure was well tolerated.

The following day the patient was well. Repeat LFT showed an elevated Bilirubin at 124, and Alkaline Phosphatase (AP) of 670 and an Aspartate Transaminase (AST) of 76. The serum amylase remained within normal limits. A contrast enhanced CT scan at 24 hours showed the tumour to measure 4.5 x 4 x 4 cm within which was an area of non-enhancement measuring 4 x 3 x 3 cm (Figure 7.07b). Thus a significant proportion of the tumour volume had been rendered ischaemic. The patient was then discharged with a view to repeat treatment in 3 weeks time targeting the inferior portion of the tumour.

The patient was readmitted as an emergency 2 weeks later with abdominal pain, fever and confusion. LFT at this stage revealed a Bilirubin of 90, AP of 1303 and AST of 286. In addition, the white cell count was markedly elevated with a profound neutrophilia. These findings suggested increasing cholestasis with an element of hepatocellular necrosis possibly secondary to sepsis. Blood cultures grew Clostridia Perferingens which was treated with triple therapy antibiotic therapy. An US confirmed decompressed intrahepatic ducts with the stent apparently in a satisfactory position. However, the common bile duct and gall bladder appeared to be dilated. The provisional diagnosis was ascending cholangitis possibly due to inadequate stent drainage. At ERCP, tumour was seen

infiltrating the duodenal cap in addition to dilated air filled common and intrahepatic ducts. Free flow of contrast through the stent into the biliary tree was demonstrated although no information relating to filling of the cystic duct or gall bladder was provided. The patient condition failed to improve prompting a CT scan 1 week from admission. Pneumobilia was noted with a massive collection occupying much of the right hepatic lobe. The common hepatic artery was patent. The tumour measured 5 x 4 x 5 cm with a non-enhancing area measuring 3 cm in diameter. Five hundred milllitres of blood stained pus was aspirated under US control using a pigtail catheter. Subsequent cultures grew Streptococcus Faecalis. A tubogram showed no communication between the cavity and the biliary tree raising the possibility of haematogenous origin to the sepsis. Four sequential CT scans at roughly weekly intervals showed persistence of the right lobe abscess confirmed clinically by continued drainage. The pancreatic tumour continued to grow reaching 6 x 6.5 x 5.6 cm by 8 weeks from laser treatment. A residual area of non-enhancing tumour measuring 3 cm in diameter persisted. However, the patient's condition remained poor with increasing confusion and erratic blood sugars.

A final CT scan 6 weeks from admission showed multiple hepatic abscesses in both lobes associated with a distended gall bladder containing gas. Bilateral pleural effusions and ascites were also noted but culture of the later yielded no growth. Percutaneous drainage of the gall bladder revealed a sterile serosanguinous fluid. The patient's condition continued to deteriorate with progressive drowsiness and declining renal and hepatic function. The patient died 7 weeks from admission from overwhelming sepsis due to multiple hepatic abscesses. A post mortem was not performed. It is important to note that at no stage during the patient's septic illness was there any evidence of sepsis in the pancreas

7.4 DISCUSSION

The prognosis for pancreatic cancer remains poor. In 10 to 15% of patients, surgery is feasible and offers the only hope of cure. Few patients unsuitable for surgical resection are offered any form of palliative therapy to control local tumour growth. Current palliative techniques effective in achieving local control are invasive. Patients unfit for general anaesthesia are excluded while retreatment of those who relapse is impractical and

limited by tissue thresholds to radiotherapy. In addition, current palliative methods remain the province of a handful of enthusiasts, with complex and protracted regimens compromising quality and duration of a limited survival time.

This pilot study attempted to address these problems by assessing the feasibility and safety of ILH in treating localised pancreatic cancer. Applied percutaneously, ILH proved simple to perform under US control with tumours relatively well visualised as areas of mixed echogenicity. Ultrasound and CT proved to be complimentary modalities in assessing tumour margins and the extent of any laser mediated necrosis. The needles could be inserted into the tumours with relative precision by an experienced interventional radiologist. The needles transgress the transverse mesocolon producing no obvious ill effect in the short term. One possible complication is needle tract seeding which has been well documented for pancreatic cancer (Smith., 1980, Smith., 1984, Livraghi et al., 1983). In the main, this remains a theoretical risk as temperatures generated around the fibre and needle tips are in excess of 100^{o}C. Thus, any tumour cells shed along the needle tract from the treatment zone are likely to be non-viable. In theory, clumsy needle placement and withdrawl without laser treatment in an attempt to achieve perfect placement could pose a risk. Treatments were in general well tolerated producing radiological evidence of tumour necrosis in all patients. In this small series, fears concerning acute pancreatitis and fistula formation were unfounded. None of the patients demonstrated significant elevation in the serum amylase following treatment reflecting the precise localization of the thermal damage to the tumour. Despite evidence of least partial necrosis, the tumours continued to grow with all patients dying from extensive local and disseminated disease within 9 months from treatment. Admittedly, non-viable tumour volume formed a small proportion of total tumour volume in these patients. This was due in part to our cautious initial approach so that no deliberate effort was made to treat any of the tumours in their entirety. It seems unlikely that laser treatment had any significant influence on disease progression due to two factors. The extensive nature of local disease on initial laser treatment in addition to occult disseminated disease which is beyond the scope of laser or any other regional treatment. Uncontrolled distant disease is likely to have been a significant cause of patient mortality in this series.

Acute obstruction of the common bile duct occurred in the second patient ten days following laser treatment probably as a consequence of an acute inflammatory response and tissue oedema around the pancreatic head. The common bile duct was successfully decompressed with an endoprosthesis. However, it would be prudent that patients with tumours in or near the head of the gland who have not had a biliary enteric bypass should have an endoprosthesis inserted before laser treatment. The third patient developed a chronic upper gastrointestinal bleed which appeared to be self limiting. Careful endoscopic and post mortem examination failed to demonstrate a source. It is unlikely that angiography would have localised the source given the slow rate of bleeding although a labelled isotope red cell scan may have helped. In all probability, it seems unlikely that the bleed was a direct manifestation of laser treatment. The post mortem allowed for the first time macroscopic and histological confirmation of the radiological features of laser induced necrosis of pancreatic tumour. Thus non-enhancing tumour on contrast CT and cystic changes on US accurately represented the extent of necrotic tumour. Further work correlating the radiological and pathological extent of tumour necrosis is required to confirm this initial favourable impression.

It is interesting to speculate on the cause of bleeding seen in the fourth patient. Certainly the duodenal wall is close to the area of tumour devascularisation produced by laser treatment and therefore it is conceivable that thermal damage leading to ischaemic ulceration may have produced the endoscopic appearances seen. However, it is curious that the ulceration was circumferential since one might expect thermal energy to be propagated up and down the medial duodenal wall thus confining the damage to that area. It seem fortuitous there was no free perforation of the duodenal wall. Gastroscopy is only able to assess the mucosal aspect of the duodenum which may have been selectively damaged with preservation of the muscular and serosal elements thereby maintaining duodenal integrity. Given the extensive area of tumour avascularity, it is likely that the distal end of the common bile duct may should have been damaged yet there was no overt manifestation. A possible explanation is that the common bile duct is occluded above the level of the damaged area with bile passing perferentially through the cholecysto-jejunostomy. Common bile duct damage may be of greater significance in those patients with patent ducts

and no diverting biliary conduit. In the absence of biopsies showing tumour it is difficult to reach a conclusion on the cause of the duodenal ulceration. However, a negative biopsy may merely indicate a sampling error or that biopsies taken were too superficial.

The ultimate fate of avascular tumour produced needs to be followed up with repeat CT scans with guided biopsies to confirm the radiological changes seen are infact irreversibly damaged tumour tissue. In addition, correlating the healing pattern of the tumour as indicated radiologically is necessary. Repeat gastroscopy with further biopsies of the abnormal duodenal area would be useful. However, the demise of the patient who resided in the United States prevented further follow up or a post mortem.

The last patient in the series poses an interesting problem in defining the sequence of events leading to his demise. There are three possible mechanisms leading to sepsis of the right liver lobe.

1) Reflux of infected pancreatic juice up a patent stent originating from infected necrotic tumour.

2) Haematogenous via the arterial or portal circulation.

3) Ischaemic necrosis of the right liver with secondary infection.

In the presence of a functioning stent as demonstrated at ERCP, it would seem unlikely that there was significant reflux of infected bile into the intrahepatic biliary radicles. By the same token, it is possible that necrotic tumour following laser treatment became colonised. As a consequence, infected pancreatic juice refluxed up a patent stent. Indeed, if this was the case then multiple bilobular abscesses would have been most likely. This was not the case until the terminal stages of the patient's illness. In any event, a tubogram performed showed no communication between the abscess cavity and the biliary tree. This also excludes the obstructed gall bladder (due to an occluded cystic duct) as the septic focus. There was no evidence at any stage of the patient's septic illness of infection within the pancreas making it very unlikely as the source of sepsis. The idea of haematogenous spread is similarly difficult to entertain given the selective manner of right lobe involvement. A more plausible sequence of events is that following laser therapy, the right hepatic lobe became necrotic with secondary colonisation from the portal blood stream. The mechanism of right lobe necrosis can only be a matter for speculation. A

possible explanation relies on anatomical variations in hepatic vasculture which are well described. In 20% of individuals, the right hepatic artery is derived directly from the superior mesenteric rather than the common hepatic artery. When so replaced, the whole blood supply to the right lobe is derived from the superior mesenteric artery. It is therefore possible that such an anomalous right hepatic artery may be damaged by heat diffusing from the tumour during treatment. Immediate or subsequent thrombosis may have lead to ischaemic damage despite a contribution from the portal circulation. Elevation of the AST in the post treatment period would have added weight to such a theory. However, the patient was discharged the day following treatment apparently well, therefore, no AST estimations are available. A mesenteric angiogram would have helped to refute or confirm an abnormal hepatic circulation but this was not done. Post mortem study of hepatic vasculture was not possible as an autopsy was not performed.

It has to be said that a converse argument could be applied to the theory of a thrombosed right hepatic artery. It is possible to ligate the right hepatic artery without any untoward damage to the right lobe. In addition, if heat did diffuse to a sufficient extent to reach the vessel, in all probability the high blood flow with such a relatively large vessel would make an effective sink conducting heat rapidly away into the general circulation with little or no damage to the vessel wall. However, the fate of a blood vessel adjacent to a heat source must depend upon a balance between the rate of thermal energy reaching it and its ability to dissipate the heat as a function of blood flow. In the case of this patient, local anatomy, tumour and fibre position may have tipped the odds in favour of vessel occlusion. Not with standing the serious complication that arose in this unfortunate patient which may be laser related, the tumour continued to increase in size despite an admittedly incomplete treatment.

No patient in this series demonstrated a reduction in tumour dimensions despite achieving necrosis in a significant volume of tumour in the last two patients. A possible explanation is the highly scirrhous nature of pancreatic cancer preventing remaining viable tumour from shrinking once the centre has undergone necrosis. Radiologically, necrotic tumour is therefore visualised as cystic areas.

The maximum benefit of ILH is likely to be achieved with small (diameter ≤ 3 cm) localized tumours in the absence of metastatic spread, although the resolution capability of current imaging modalities in detecting such tumours is a significant limiting factor. At present, such tumours which are resectable should be dealt with by surgery. When surgery is contraindicated, the results of this pilot study are sufficiently encouraging to suggest that ILH may have a role in arresting primary tumour growth. Unfortunately, the vast majority of patients have disease beyond the confine of the pancreas which clearly cannot be dealt with by ILH. Optimum local palliation will require development of effective adjuvant chemotherapy to deal with nodal and microscopic peripancreatic deposits and distant metastases. In addition, research in several directions is necessary to refine the efficacy of ILH. Matching the extent of laser mediated necrosis accurately to the tumour remains the keystone of producing the most effective palliation. Improvement in imaging techniques allowing better resolution of the true extent of a tumour are therefore necessary and may be provided by CT or MRI. A study correlating the pre-operative radiological and macroscopic dimensions with measurements of resected tumours would go some way to achieving this. Similarly, the significance of real time changes seen sonographically require further evaluation in an attempt to define reliable end treatment points. It is likely that CT and or MRI may supersede ultrasound as the real time imaging modality of choice. Ultimately, the challenge of a thermo-chemotherapeutic approach will be to match or improve on local recurrence rates achieved with surgery at minimal morbidity and mortality perhaps with a measurable improvement in survival.

Finally, it would be beneficial to contrast ILH in the liver and pancreas. The anatomical and physiological features of these two organs contrast markedly. The liver is a large intraperitoneal organ with few adjacent vital structures while the pancreas is a relatively small retroperitoneal organ with many adjacent vital structures such as the common bile duct, portal vein, duodenum, superior mesenteric vessels and overlying transverse colon and mesocolon. The functional and regenerative capacity of the liver are huge compared to the pancreas which is capable of healing only by scar tissue. These considerations mean the liver can be visualised radiologically and accessed percutaneously with greater ease and safety. For the pancreas, the close proximity of so many important

structures calls for accurate needle placement and precise localisation of the zone of necrosis to avoid their inadvertent damage.

Sonographically, tumour necrosis within the liver 2 to 4 weeks from laser treatment is virtually indistinguishable from untreated tumour. In contrast, necrotic pancreatic tumour appears as cystic areas within surviving tumour. The mechanism of repair of laser indued necrosis in different. The liver heals by resorption of the necrotic tissue with healing by regeneration. For the pancreas, necrotic tissue is replaced by scar tissue. CT follow up after successful tumour eradication with complete healing is likely to show a non-enhancing (avascular scar tissue) area in the pancreas as a legacy of the previous tumour site. For the liver, the previous tumour site is likely to have the same attenuation pattern as the surrounding normal liver. Histologically, one would expect on biopsy normal liver and fibrous tissue from the liver and pancreas respectively.

CHAPTER 8. INTERSTITIAL LASER HYPERTHERMIA FOR BREAST CANCER

Few areas of surgical practice attract as much controversy as the management of breast cancer. The situation has improved in recent years with the optimum management of early breast cancer being slowly defined. It may therefore, seem presumptuous to suggest that a new technique such as ILH may have anything new to offer in the local control of early breast cancer. Is this not likely to muddy waters which have only just began to clear ?

With any new technique, it is important to consider the strength and weakness of conventional treatment to identify where the new method may offer any useful advantage which can be exploited practically. I shall therefore, start with a brief review of currently accepted ideas in the management of early breast cancer, that is disease limited to the primary site with or without axillary node involvement on the ipsilateral side.

8.1 BACKGROUND

Breast cancer is the commonest malignant disease of women in Great Britain. One in 12 women develop a carcinoma of the breast which accounts for approximately 15,000 deaths in any one year (Mansell., 1988). The 5 year survival rate is approximately 75%, but of the 5 year survivors, 17% will die in the following 5 years (Young., 1989). Management aims to control disease locally, prevent the development of metastases and prolong life with as little morbidity, cosmetic or psychological disturbance as possible.

In 1894, Halstead demonstrated in a controlled non-randomized trial that local recurrence rates from breast cancer could be improved from 50-80%, with wide excision alone to 6% with a 'radical mastectomy' (Halstead., 1984). Until the early 1970s, the standard treatment for early breast cancer has been total mastectomy with axillary lymph node dissection. Those with histologically positive nodes went on to receive radiotherapy to the chest wall, axilla, internal thoracic and supraclavicular nodes. Good control with local recurrence rates of 7% were achieved (Host et al., 1986). However, this approach had its problems. All patients lost the whole of the affected breast with its associated psychological sequelae. Morbidity was common especially lymphoedema of the arm

affecting up to 80% of patients depending on the extent of axillary surgery (Yeoh et al., 1986). In a meta-analysis of randomised trials, addition of radiotherapy appeared not to improve survival possibly due to the complications of myocardial and pulmonary fibrosis that can follow radiotherapy (Yeoh et al., 1986)

The notion that aggressive surgical clearance of local tissue improves long term survival has recently been re-evaluated. Breast cancer is increasingly being regarded as a systemic disease from the outset with control of micrometastases the cornerstone to long term survival. The role of primary surgery has shifted in its objective with preservation of the breast if possible yet remain effective in preventing locally recurrent disease.

BREAST PRESERVING SURGERY

Several trials have compared total mastectomy with axillary lymph node dissection (radical mastectomy) with breast preserving surgery; that is either a quadrantectomy or lumpectomy with histologically free margins combined with axillary lymph node dissection followed by radiotherapy to the breast (Veronesi et al;.,1986, Fisher et al., 1989, Van der Schueren et al., 1988). Omission of radiotherapy increased the rate of local recurrence. The broad thrust of this work has shown that for patients with tumours less than 4 cm in diameter, then a conservative approach can produce local recurrence and survival rates comparable to those achieved with more radical surgery.

Factors predisposing to local recurrence in patients treated conservatively are important to define. They are likely to be instrumental in determining local recurrence rates if ILH is used as a primary treatment aimed at local control of early breast cancer. Incomplete excision and the presence of extensive intraductal carcinoma were positive risk factors for local recurrence following conservative surgery (Van der Schueren et al., 1988). Controversy surrounds the extent of macroscopically tumour free margin that should be incorporated around the primary tumour. This has clear implications for ILH treatment as to the extent of apparently normal tissue around the primary tumour that would have to be incorporated into the treatment zone if laser therapy was employed. One study suggested that a minimum rim of 1 cm around the primary lesion should be removed (Veronesi et al., 1990). Even then, one report estimated that foci of tumour would remain in 59% of

patients (Holland et al; 1985). Although it is unclear whether all foci can give rise to clinical recurrence, it is likely that prevention of local recurrence in this group of patients might depend heavily on the efficacy of radiotherapy or other adjuvant therapy such as tamoxifen. It may be better to increase the tumour free margin of excision/treatment to 3 cm where the probability of persistent tumour falls to 17%.

Relative contraindications to breast preserving surgery include extensive intraductal permeation or mammographic evidence of multicentric disease. In addition, tumours greater than 4 cm in diameter particularly in small breasts or underneath the nipple where the cosmetic result is likely to be unsatisfactory. Extrapolating these contraindications to ILH, then clearly the first two must apply. However, tumour diameter *per se* would probability not constitute a contraindication; in theory, there is no limit as to the number of fibres that can be used which could be tailored to tumour dimensions. The atraumatic and minimally invasive nature of ILH could make it particularly suited to treating relatively large tumours in small breasts with an acceptable cosmetic outcome.

PSYCHOLOGICAL SEQUELAE

Much is made of the psychological morbidity caused by the mutilation of radical breast surgery. In theory, breast preserving surgery causing less cosmetic deformity should be more acceptable to the patient. The ultimate goal must be effective treatment without scarring as may be possible with ILH. However, the psychological effects of no scar treatment or breast preserving surgery may not necessarily be less than following radical mastectomy.

One study investigated the incidence of anxiety and depression in 101 women up to 2 years following randomisation to radical mastectomy or breast preserving surgery (Fallowfield et al., 1986). The patients had expressed no strong preference for one treatment over another. Anxiety, depression or both was present in 38% of those treated by lumpectomy compared with 33% who had a radical mastectomy. The source of fear in the two groups varied. Those treated by lumpectomy were fearful of a recurrence while those treated more radically were more concerned about the influence of the operation had on their relationship and appearance. This study brings into question the premise that breast

preserving operations lessens the psychological impact of surgery. By the same token, this point should be borne in mind when exalting the psychological benefit of a no scar treatment. It is clear that many women feel that there are given inadequate information about their illness and its treatment. Improved councelling with more say in treatment choice may make patients less prone to anxiety and depression.

TREATMENT OF THE AXILLA

The biological effect of ILH is merely a function of fibre position. Herein lies its weakness; its therapeutic benefit can only target the primary lesion in the breast leaving the axilla untreated. However, the situation is not so simple, for management of the axilla in early breast cancer remains controversial (Sacks et al., 1992). Surgical treatment of the axilla is traditionally aimed at prevention of local recurrence and determining axillary node status. The latter remains one of the most important prognostic factors in early breast cancer determining staging and rational use of adjuvant systemic therapy.

Local recurrence is more likely although by no means inevitable if involved axillary nodes are left untreated. Though often treatable, local recurrence is demoralising for the patient. Axillary recurrence can be effectively prevented using either radiotherapy or complete axillary dissection (Van der Schueren et al., 1988). Combining both produces unacceptable morbidity. Since axillary nodal status cannot be reliably determined clinically, only surgery can provide histological and prognostic data as well as preventing local recurrence. Efficacy of disease control in the axilla and the quality of histological data depends on whether axillary clearance or limited sampling is performed and the skill of the surgeon (Benson & Thorogood., 1986). However, in experienced hands, axillary sampling can provide reliable data with low morbidity (Sacks et al., 1992). A important proviso is that improved survival has not been unequivocally shown with axillary clearance (Cabanes et al., 1992). A recent prospective trial randomised women with small breast tumours and absent axillary node involvement as determined by palpation to lumpectomy alone or with axillary dissection. Both groups received radiotherapy. Five year survival rates were superior in the axillary dissection group although this could be attributed to adjuvant therapy given to those who have positive nodes.

Most post menopausal women are currently offered tamoxifen regardless of nodal status. The argument for axillary dissection is perhaps less strong for these patients who could constitute a favourable group for ILH treatment. Other options include a wait and see policy treating those who develop axillary recurrence (surgery or radiotherapy) following treatment of the primary lesion (surgery or ILH). An alternative is to irradiate the axilla routinely after treatment of the primary cancer. However, this would overtreat a significant number of patients and deny information affecting prognosis.

From the above review, breast preserving surgery can provide highly favourable local recurrence and long term survival rates. Taking this concept of breast conservation a step further, it would seem reasonable to attempt in selected cases *in- situ* destruction of small clinically localised breast tumours using ILH. In theory, this may avoid the physical and psychological morbidity associated with surgery. This non-surgical approach can be combined with appropriate treatment in the form of radiotherapy to the breast and axilla. The superficial location of the breast and the ease of visualising solid lesions within it using ultrasound (admittedly only to a resolution of 5 mm in diameter) makes ILH an attractive technique to consider. The role of ultrasound is to define the limits of the tumour, guide needle placement and monitor in real time changes in tumour echogenicity.

Two patients were initially treated by percutaneous ILH under ultrasound guidance. The first patient refused all forms of conventional treatment for her localised breast carcinoma, while the second patient had an uncontrolled local recurrence with extensive metastatic disease. In both patients, considerable regression in tumour size was observed clinically. Whilst encouraging, such a therapeutic strategy is unsound. Optimum results will only be achieved by matching the extent of laser mediated necrosis to tumour volume. As yet, no study has correlated the nature and extent of laser mediated tumour necrosis with applied laser parameters. To address this problem, the following clinical study was initiated. Patients with histologically proven palpable carcinomas clinically localised to the breast were treated using ILH several days prior to surgical excision. The operative specimen was assessed histologically to correlate the extent of laser mediated necrosis with the treatment laser parameters. This study was granted local ethical committee approval.

8.2. METHOD

Over a 12 month period, 14 patients seen in a routine breast clinic with newly diagnosed early breast cancer were asked if they would undergo ILH prior to their surgery. Nine patients agreed. All patients were given a full explanation as to the nature and aims of laser treatment with emphasis on the experimental nature of the technique. Despite no clear benefits to the participating patients, all were happy to be involved in this unique study in the knowledge that through their misfortune, they may be helping future patients. It was made clear to all patients that they could withdraw from the study at any time without fear for the quality of their future treatment. Informed consent was thus obtained from all patients.

Mean patient age was 59 years (range 39 to 79). The average tumour diameter as assessed by palpation was 3.0 cm (range 2.0 to 5.0 cm). Seven of the 9 tumours were located in the upper outer quadrant, with the remaining two located close to the nipple in the inner half of the breast. Clinically, no tumour was attached to skin or the underlying pectoralis major muscle. No patient had palpable axillary lymph nodes or detectable distant metastases on staging (Liver function test, serum calcium, chest radiograph, ultrasound of the liver, isotope bone scan). All patient had a mammogram with a fine needle aspiration biopsy or a core biopsy prior to laser treatment. Histological examination of the operative specimen revealed all tumours to be invasive ductal carcinomas.

All patients were treated using a continuous wave Nd:YAG laser (Flexilase, Glasgow) coupled to a 4 fibre 200 micron canstar delivery system. The laser and fibres were prepared in an identical manner to that described in chapter 5. All treatments were performed on a day case basis. Under aseptic conditions, the tumour, overlying skin and surrounding tissues were infiltrated with 5 to 10 ml 2% plain lignocaine. The tumour was located using a 7.5 MHz ultrasound probe (Aloka 650, Japan). One or more hollow 19 Gauge needles were inserted percutaneously into the tumour centre under ultrasound control (Figure 8.01). When more than one needle was used, then they were placed in juxtaposition with a separation of approximately 1 cm to minimise the possibility of non-treatment of intervening tumour tissue. A suitably prepared fibre from a 4 fibre 200 micron fibre coupler was inserted down each needle so that 2 to 3 mm of bare fibre protruded

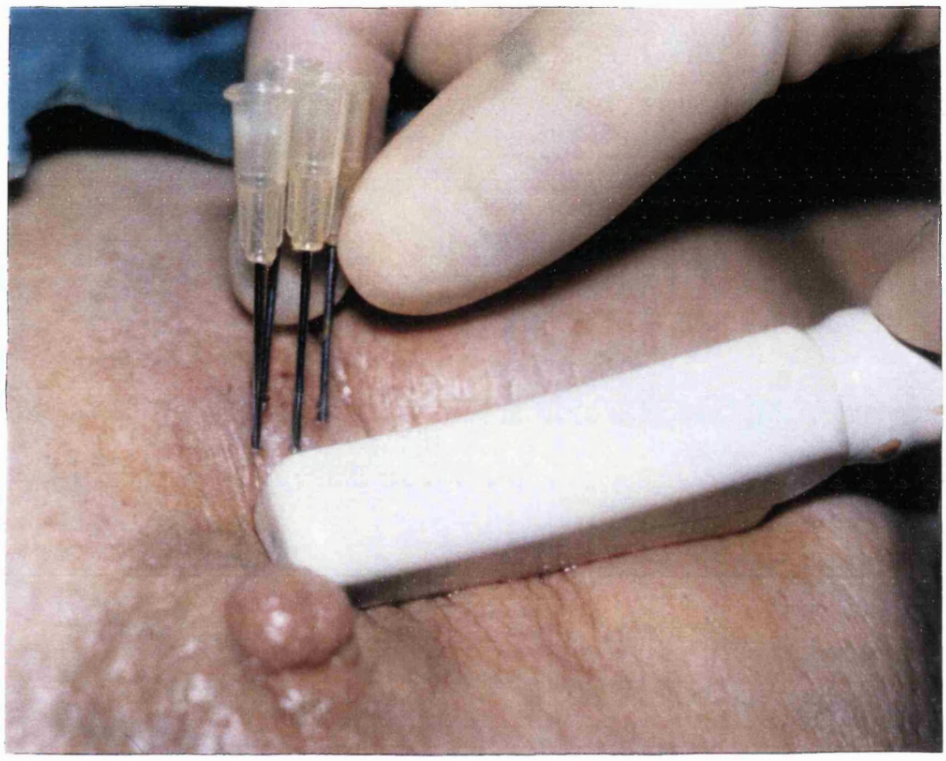


Figure 8.01. Percutaneous needle insertion into a breast tumour under US guidance.

beyond the needle tip to lie within the tumour. The laser which had been preset to a power of between 1.5 to 2.2 watts per fibre was fired for up to 500 seconds. The ensuing thermal changes were monitored in real time using US. Despite apparently satisfactory fibre placement, the procedure had to be abandoned in two patients due local discomfort and heat around the needle puncture sites. The treatment was otherwise completed successfully in the remaining 7 patients. At the end of the procedure, the needles and fibres were removed and Bonneys blue ink applied at the skin puncture sites to help subsequent orientation of the fibre position in relation to the tumour. A dry dressing was then applied to the puncture sites. The patients were allowed home to be readmitted at a later date for definitive surgical treatment. The time interval from laser treatment to surgical excision was 24 hours in 5 patients and 7 days in the remaining 2. On readmission, the patient was examined. The treated breast was inspected and palpated to detect any change in tumour size or consistency, any evidence of sepsis or thermal damage to the overlying skin. With the exception of one patient who was treated by radical mastectomy, all patients received wide local excision of their tumours. The surgical specimen was analysed independently by an experienced breast pathologist to assess the macroscopic and histological extent of laser mediated necrosis.

8.3 RESULTS

Of nine patients treated, 2 patients found the procedure intolerable within a short time of laser activation despite what appeared on ultrasound to be adequate fibre placement within the tumour. No further attempt at treatment was made. Seven patients successfully complete the laser treatment with minimal discomfort described as a sensation of warmth in the treated breast which was easily tolerated. Subsequent histological examination of the operative specimen in one patient revealed that the laser fibre had missed the tumour completely while the surgical specimen of a second patient was received piecemeal so that no meaningful evaluation could be made. Thus histological examination was possible in only five of the seven patients who completed the laser treatment.

All tumours were easily detected on US appearing as hypoechogenic areas with irregular rather spiculated margins (Figure 8.02a). This allowed relatively accurate needle

placement within the tumour and relative to each (Figure 8.02b). The patient in which the laser fibres missed the tumour was one of the first in the series and I can only attribute this to my inexperience. During photocoagulation, a gradual hyperechogenic change developed around each of the fibres and coalesced so that immediately at the end of treatment the tumour appeared hyperechogenic at the treatment site (Figure 8.02c). This feature was most prominent at the higher treatment energies (> 1000 joules).

Macroscopic and histological examination of all resected specimens revealed evidence of at least partial tumour necrosis which was roughly spherical, well defined and centred around the fibre tip. Table 8.01 summarises the dimensions of tumour necrosis as related to treatment energy.

PATIENT	*TUMOUR SIZE (MM)*	*LASER ENERGY (JOULES)*	*NECROSIS AREA (MM)*
M.L	*30 X 30*	*850*	*5 X 5 X 4*
R.B	*20 X 20*	*900*	*7 X 7 X 5*
M.M	*25 X 20*	*1200*	*8 X 4 X 6*
J.P	*25 X 25*	*1500 **	*12 X 7 X 10*
*I.S ***	*20 X 20*	*1800 **	*23 X 21 X 20*

** No viable tumour in operative specimen * 2 fibres used

Table 8.01. Relationship of tumour size and extent of necrosis.

Macroscopic examination of the tumour showed a small focus of charring around the fibre tip site surrounded by a well defined zone of tumour coagulative necrosis which was inturn surrounded by a halo of haemorrhage and oedema (Figure 8.03). Light microscopy of haematoxylin and Eosin stains of the tumour revealed a central charred zone with a small area of cavitation (Figure 8.04). Clumps of non-viable tumour cells lay in a haemorrhagic exudate with sharp demarcation between viable and non-viable tumour. The assessment of viability was made on morphological appearance of the tumour cells on high power (x 80) by an experienced breast pathologist. Deep staining pyknotic nuclei were

Figure 8.02a.

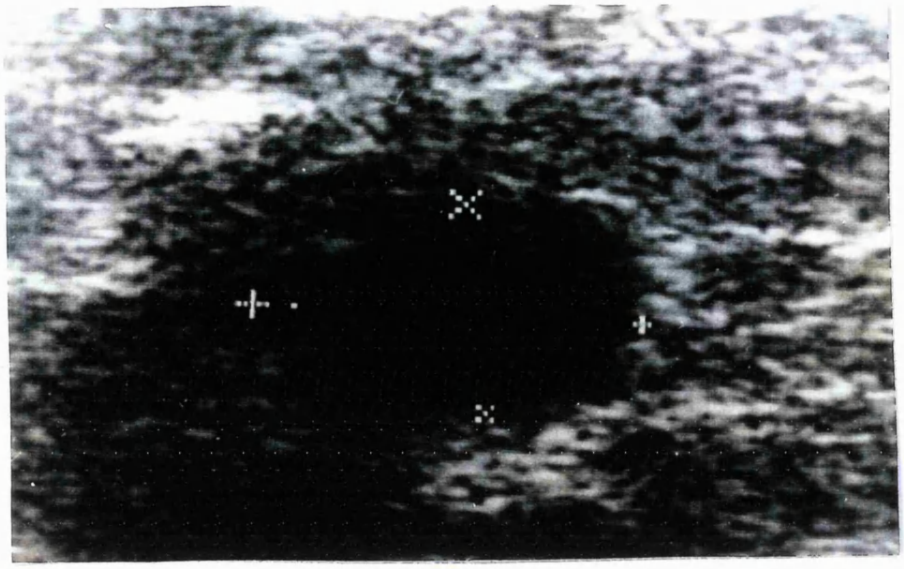


Figure 8.02b.

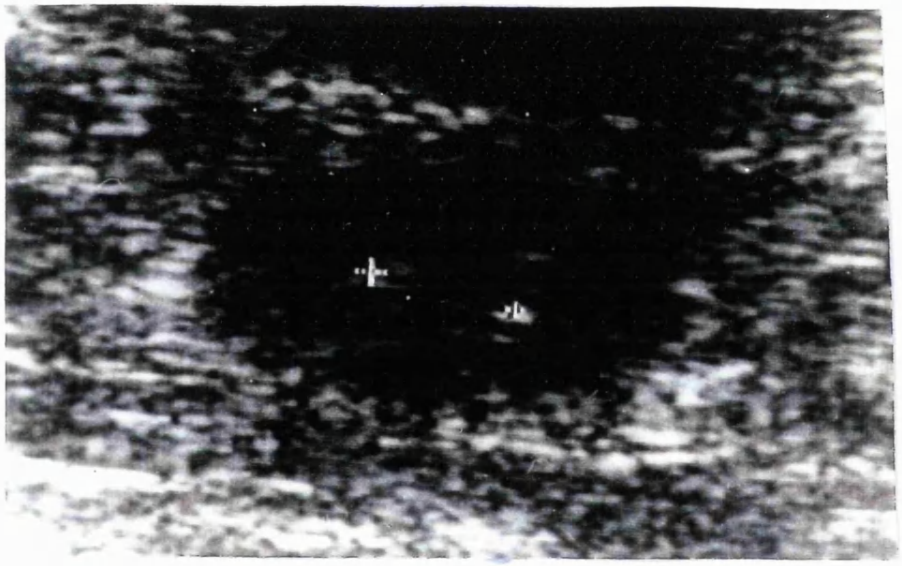


Figure 8.02c.

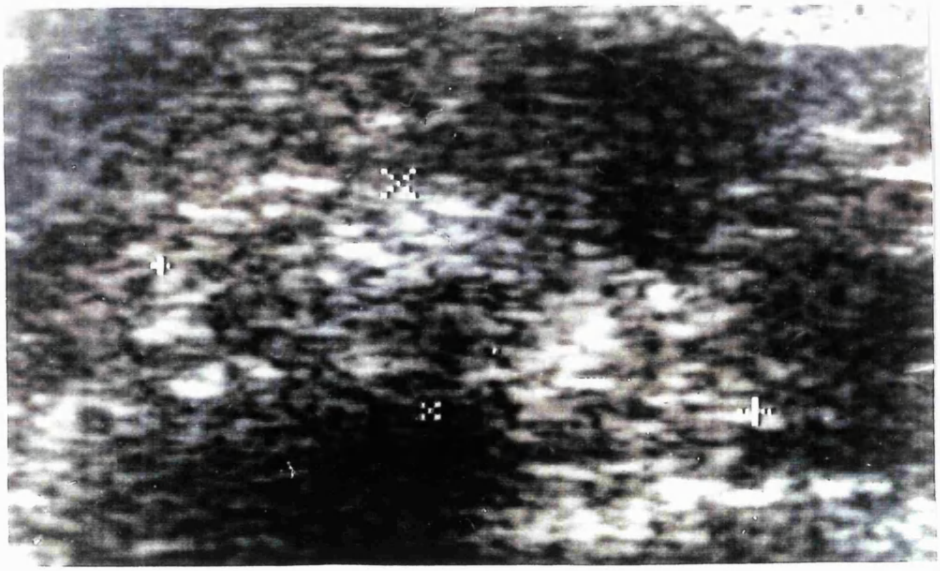


Figure 8.02a. US appearance of a 2 cm breast tumour (+.....+) (x.....x) which appears hypoechogenic with relatively poorly defined margins.

Figure 8.02b. The same tumour following insertion of 2 needles. The needle tips (+) can be seen as hyperechogenic foci within the tumour centre.

Figure 8.02c. The tumour (+.....+) (x.....x) immediately following treatment. In contrast to figure 8.02a, the tumour appears hyperechogenic reflecting the extent of laser mediated damage.

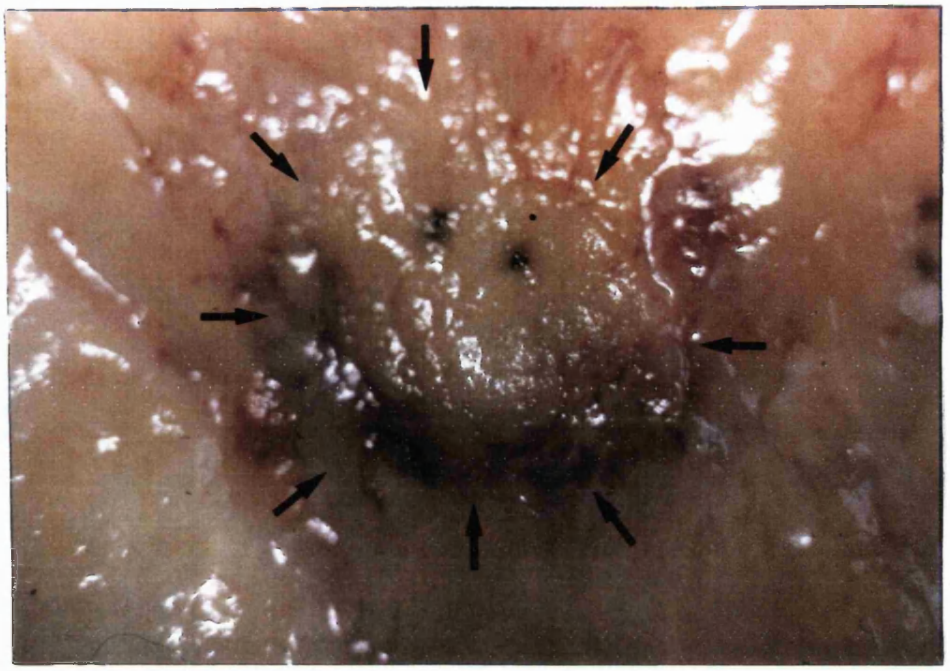


Figure 8.03. Naked eye appearance of a 2 cm breast tumour (arrowed) 1 week following treatment. Fibre position is denoted by the small foci of charring surrounded by a well defined area of coagulative necrosis and a halo of oedema and haemorrhage.

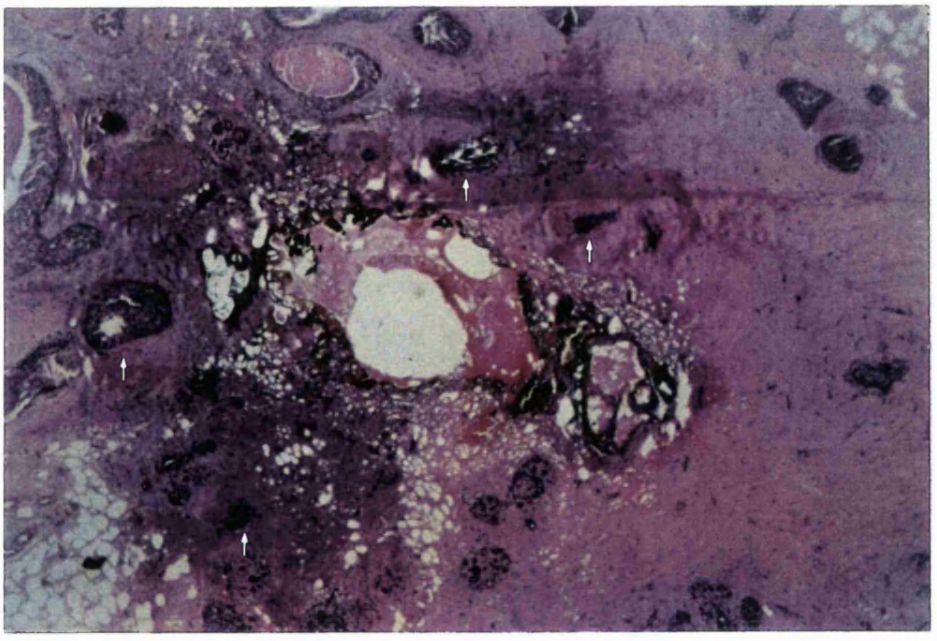


Figure 8.04. Low power histological appearance of figure 8.03 (H&E stain). There is a central area of cavitation and vacuolation surrounded by a zone of charring. Clumps of non-viable tumour cells are arrowed.

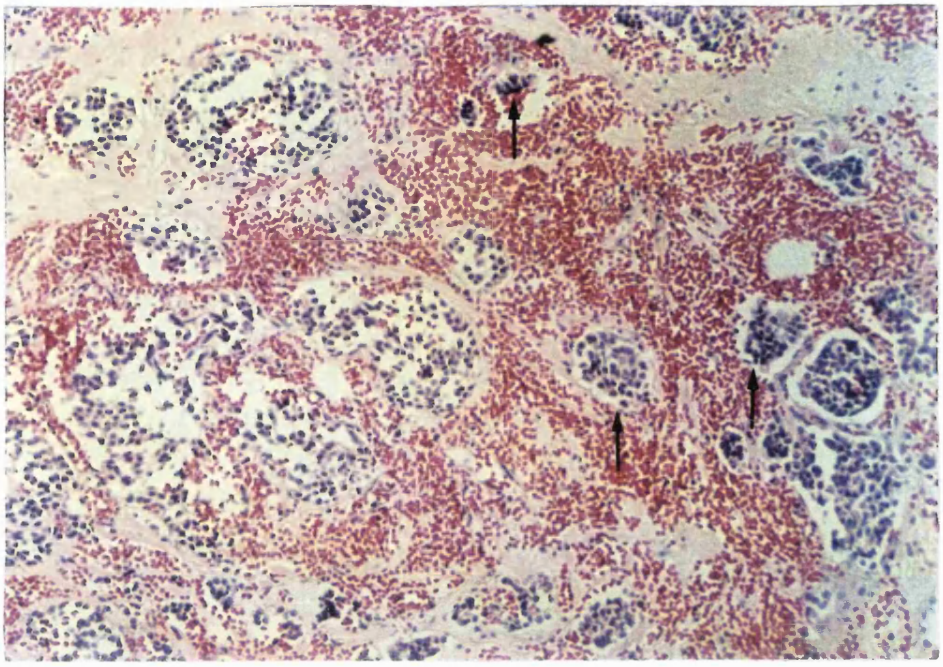


Figure 8.05. High power view of non-viable tumour cells following laser treatment (H&E stain). The tumour cells lie within a haemorrhagic exudate and have deep staining pyknotic nuclei.

taken as an indication of non-viability (Figure 8.05). The maximum extent of tumour necrosis ranged from 5 mm using 850 joules up to a maximum of 22 mm using a treatment energy of 1800 joules. The mean necrosis diameter was 10 mm. A 20 mm diameter cancer was totally non viable in its entirety on multiple histological sections.

The only complication seen was a small partial thickness dermal burn around the needle entry site. This is due to heat conduction along the needles from the fibre tips which act as a heat source.

8.4 DISCUSSION

This small pilot study has shown that ILH is a feasible technique for inducing necrosis in early breast tumours. The technique is simple to perform, in the main is well tolerated and can easily be carried out on an a day case basis. Two patients complained of excessive pain shortly following activation of the laser. This is difficult to explain given two findings. The operative specimen showed no evidence of laser mediated tumour damage. Secondly, wayward needle placement leading to inadvertent treatment of the underlying muscle seems unlikely as needle tracts extending to but not beyond the tumour were noted in the operative specimens. Both patients were understandably anxious over a newly diagnosed potentially lethal malignancy. This anxiety can only have been hightened by being subjected to a new untried treatment.

The choice of laser powers, treatment times, fibre number and separation were to a large extent empirical. It has to be said producing complete tumour necrosis in the last patient was purely by good fortune. In no patient was there any specific attempt to treat the tumours in their entirety. In principle, this study indicates that once the appropriate laser parameters are defined and related to tumour volume, ILH has the potential to completely destroy small breast cancers *in-situ.* with no cosmetic deformity to the breast. In theory, treated breast tumours should heal by resorption and fibrosis. It is debatable whether scarring would leave a palpable lump which may be an unacceptable source of anxiety for some patients.

However, it is clear that further work on dosimetry, laser fibre position and separation is necessary to determine the optimum treatment parameters that can confidently predict complete destruction of a breast tumour of any given volume. A further point worth mentioning is that the far infra red wavelength of the Nd:YAG laser (1064 nm) is best suited to treating highly pigmented well vascularised tissue. Treating a suitable laboratory tumour model using a variety of shorter laser wavelength (for example, the new generation of semi-conductor lasers) may yield a more suitable laser wavelength for producing necrosis in the acellular, relatively avascular and non-pigmented breast tumours seen in clinical practice.

At the risk of labouring the point which has been emphasized before, the fundamental principle of ILH in oncology is to match the extent of laser mediated damage to tumour volume. Ignoring this will inevitably lead to poor clinical results. The situation in breast cancer is complex. Reports from the surgical literature estimate that foci of tumour remain in 59% and 17% of patients if tumour free resection margins of 1 cm and 3 cm respectively are taken (Veronesi et al., 1990, Holland et al., 1985). This would suggest that good results from ILH will only be achieved if the zone of laser mediated damage incorporates a rim of apparently normal breast tissue in excess of 1 cm. Clearly, visual access to the tumour is denied using ILH. We are therefore highly dependant on imaging to act as our eyes. In this study, given its ready availability and ease of use, US was used. However, CT, NMR or even mammography may have useful advantages in resolution. What ever imaging modality is used, two questions need to be addressed. What is the correlation between the radiological or sonographic tumour extent and its true extent in the surgical specimen. In other words, is what we are seeing on imaging a true reflection of limits of the tumour or are being deceived into under or over estimating the true tumour extent. Only by answering this question can we begin to incorporate an overkill 'tumour free margin' with any precision.

The second point is identifying reliable end treatment points, that is knowing with absolute certainty that all tissue (tumour plus normal margin) within the treatment zone is necrotic. The simplest but not necessarily the most scientific is on a dose volume relationship derived from dose response curves. That is a tumour of volume X will need Y

fibres treated with Z joules. This simple approach suffers from one potential drawback. Tumours vary in their relative vascularity, therefore, hypervascular tumours may be under treated and hypovascular ones over treatment. Alternatively, is to image the tumour before, during and after laser treatment for a variable interval prior to surgical excision. By assessing the significance of the alterations in the tumour's appearance and the extent of those changes in relation to histological features, then an indication of the limits of laser mediated tumour necrosis could be made. Identification of successful tumour regression, healing and possible recurrence is essential. Thus the success of ILH is highly dependant on the quality of imaging. We have to understand what we are seeing before, during and after laser treatment if ILH is to become a useful treatment modality.

If the problems of optimum laser parameters, wavelength and imaging were to be resolved, and in theory this should be possible, what would be the role of ILH in the treatment of breast cancer ? Undoubtedly, ILH (plus radiotherapy) would first be subjected to a controlled trial against wide local excision and radiotherapy. The problem of treating the axilla will be considered later. The end points would be local recurrence rates and long term survival. Local recurrence rates might be expected to be higher with ILH due to the theoretical risk of needle tract seeding. However, the temperatures generated around the fibre tips are in excess of $100^{o}C$ therefore tumour cells seeding along the needle tract would be non-viable.

One possible role of ILH may be in debulking inoperable tumours unresponsive to or recurrent following aggressive medical treatment. Alternatively, patients with primary or recurrent local disease refusing all forms of conventional treatment may benefit. Undoubtedly, both these groups would only make up a small number of patients.

The ability of ILH to locally destroy a cancer in a breast fails to tackle the problem of the axilla. This, for most clinicians would preclude the routine use of ILH for early breast cancer. Axillary surgery yields valuable information on staging, prognosis, selecting those who would benefit from adjuvant therapy and in itself is an excellent treatment for controlling nodal disease. However, there may be alternatives which could make ILH more acceptable. The axilla could be routinely irradiated following ILH accepting that many patients would be over treated. Alternatively, a wait and watch policy could be adopted

treating the axilla (surgery or radiotherapy) only in the event of a recurrence. Another possibility would be to treat the breast primary using ILH and combine this with surgery to the axilla (sampling rather than clearance). Those with positive nodes could be offered radiotherapy. Which of these options would be best ? The answer would need to be the subject of a randomised trial. Post menopausal patients are routinely offered tamoxifen regardless of nodal status making the argument for axillary dissection less tenable. At first sight, this patient group would be favoured for ILH.

With the national adoption of screening, a large number of patients are presenting with impalpable in-situ ductal and lobular carcinomas. Much controversy surrounds the optimum treatment of this patient group. Almost all these patients are free of nodal disease and are therefore an ideal patient group for some form of breast preserving treatment in which the axilla does not need to be considered. However, there are problems. The diagnosis of *in-situ* carcinoma is made definitively from the excised surgical specimen. Treatment using ILH cannot provide the pathologist with a specimen yet it would be illogical to treat a patient blind to the tumour's true pathological grade. This denies the clinician and the patient important prognostic information which may lead to under treatment of a relatively young group of patients. A core biopsy may provide a compromise but for the moment, this is impractical for small tumours and is open to sampling errors.

It has been estimated that the incidence of multifocal in-situ disease is as high as 60% although it is unclear if all areas give rise to invasive cancers. It is not feasible to treat multifocal disease with ILH alone. Tamoxifen combined perhaps with radiotherapy would need to be considered. Alternatively, photodynamic therapy (PDT) may have a role to play. This technique relies on the administration of a harmless photosensitiser which is taken up preferentially by tumour tissue. Exposure of the sensitiser to a specific wavelength of laser light leads to release of singlet oxygen which is toxic to cells. PDT is ideally suited to treatment of organs where there is a mitotic field change. In theory, it could be used for multifocal *in-situ* breast cancer.

There are formidable problems posed by the biology of the disease, tumour imaging, dosimetry which mean, that for the moment, ILH must remain a research tool.

Much work is still needed before the idea of ILH providing an outpatient treatment for breast cancer becomes a realistic proposition.

CHAPTER 9. ILH : STUDIES IN A TRANSPLANTABLE MAMMARY CARCINOMA

9.1 INTRODUCTION

Most experimental work to date has concentrated on laser tissue interaction in normal tissue demonstrating well defined reproducible necrosis with safe healing. Amongst other factors, the way laser light interacts with tissue is an important determinant of the biological effect produced. Understanding such interactions is fundamental to the safe and effective clinical application of ILH in tumour therapy. However, it is worth noting that, in most instances, normal tissues possess different optical characteristics from their malignant counterparts due to differences in vascularity, water, stromal and pigment content.

Most clinical and experimental applications of ILH are performed using the Nd:YAG laser whose wavelength (1064 nm) is found in the infra red portion of the electro-magnetic spectrum. As has been discussed before, the biological effect of this wavelength is highly dependant upon scattering leading to secondary absorption by the treated tissues. Tissues producing extensive scattering at the near infra red wavelength are pigmented and well vascularised, for example, the liver. In clinical practice, most solid organ tumours are relatively avascular and therefore non-pigmented. As a consequence, laser tissue interaction may differ significantly if laser parameters derived in normal tissue studies are applied to such tumours. The net biological effect may be suboptimal or transgress the safety threshold for a given organ. Fundamental to the clinical application of ILH in the field of Oncology is the concept that optimum effect is derived by accurately matching the extent of laser mediated necrosis to the tumour volume under treatment. This principle goes hand in hand with trying to understand how laser light may interact with tissues of different optical characteristics.

Tumours of the same histological origin and of comparable grades can display remarkable structural heterogeneity, for example, in their stromal content. In theory, this could influence laser light interaction and the ensuing biological effect. By understanding how such factors influence the required biological effect, then the extent of laser mediated necrosis can be predicted precisely and safely to match tumour volume.

Matthewson et al (1989) attempted to redress the balance applying low power ILH from a Nd:YAG laser to treat subcutaneously transplanted fibrosarcoma using laser parameters comparable to those used on normal rodent liver. He demonstrated that once the appropriate laser parameters had been defined, complete tumour regression with significant survival benefits compared to a surgically treated and a control cohort could be achieved. However, several caveats regarding this work should be borne in mind. Tumour size was not standardised before laser treatment with a maximum variation of up to 50% in tumour diameter; this translates to significant differences in tumour volume. The extent of the biological effect for given laser parameters would vary depending on initial tumour volume which in turn could skew the survival benefits in favour of the smaller tumours. The second point is that rapidly growing experimental tumours which are biologically aggressive such as used by Matthewson can outgrow their blood supply. Cystic degeneration and spontaneous tumour necrosis can follow. Correlating tumour diameter with the presence or absence of spontaneous necrosis was not performed in Matthewson's study making it difficult to evaluate which component of tumour regression was laser mediated and which was spontaneous. This problem is further compounded by the range of tumour diameters treated which is likely to straddle the threshold beyond which central necrosis may becomes a significant factor. Given that the biological effect of Nd:YAG is dependant on tissue scattering, the presence of a central cavity may have a paradoxical effect on the extent of laser mediated necrosis. A centrally placed fibre tip within a tumour cavity will result in forward transmission of the light with minimal scattering thereby reducing the biological effect. Thus differences in tumour regression within and between cohorts could be attributable to the factors discussed above rather than different treatment laser parameters.

The work presented in this chapter addresses the problems discussed above. The first section correlates spontaneous tumour necrosis with tumour diameter in an aggressive rodent mammary carcinoma transplanted subcutaneously in the flank. The tumour is hormone independent making it suitable for use in animals of either sex. The second section assesses whether reproducibility of the extent of necrosis which has been well demonstrated in normal tissues occurs in tumours. Lastly, the influence of various laser

parameters on the biological behaviour of a subcutaneously transplanted tumour of near uniform volume and devoid of areas of spontaneous degeneration is assessed by survival. The laser parameters used in this study are comparable to those used in rodent liver by Matthewson.

9.2 RELATIONSHIP OF SPONTANEOUS NECROSIS TO TUMOUR DIAMETER

9.2.1 METHOD

Fourty adult Chester Beatty Hooded (CBH) rats (140 to 210 gms) were transplanted with a hormone independent mammary carcinoma (Hosp 9AP6, Institute of Cancer Research, Royal Marsden Hospital, Sutton, Surrey). The tumour mass was removed from the donor animal just prior to transplantation and cut into 2 mm cubes. Under a combination of halothane and oxygen anaesthesia the recipient animals were prepared. The hair on the right flank was shaved and a 5 mm incision down to the lateral abdominal wall muscle was made. A subcutaneous pouch was fashioned and a cube of tumour placed within it. The skin was closed using a 5/0 silk suture and the animal allowed to recover. Sequential transplantation was carried out to maintain the tumour line.

Each animal was caged separately and received a standard laboratory diet. Twice weekly, tumour diameter in 3 planes was measured using calipers. The tumour height was most difficult to measure reliably, therefore, any animal with a tumour diameter in the horizontal or longitudinal axis exceeding set limits was sacrificed. The animals were killed when tumour diameter reached 10 ± 1 mm (n=10), 15 ± 1 mm (n=10), 20 ± 1 mm (n=10) and 30 ± 1 mm (n=10) in any one plane. The tumour nodules were excised and sectioned several times. The extent of any areas of haemorrhage, cystic necrosis or cavitation was measured.

9.2.3 RESULTS

All tumours grew rapidly. Up to a diameter of about 10 mm the tumours grew into a spherical shape which was relatively well defined. With further growth, the tumours took on a more cylindrical shape. Tumours reached their allotted diameters of 10, 15, 20 and 30 mm in an average of 11 days (range 8 to 14 days), 17 days (range 16 to 20 days), 20 days

(range 18 to 22 days) and 27 days (range 23 to 31 days) respectively from implantation (Table & Graph 9.2.1).

ANIMAL	*10 mm*	*15 mm*	*20 mm*	*30 mm*
1	*8*	*16*	*20*	*25*
2	*10*	*16*	*20*	*27*
3	*12*	*18*	*18*	*23*
4	*12*	*20*	*18*	*25*
5	*10*	*16*	*20*	*29*
6	*8*	*16*	*18*	*25*
7	*10*	*18*	*18*	*27*
8	*14*	*20*	*22*	*29*
9	*12*	*18*	*22*	*30*
10	*11*	*16*	*20*	*31*

Table 9.2.1. Time in days from implantation to reach specified tumour diameter.

Appendix VI documents extent of tumours and any spontaneous necrosis or haemorrhage. All tumour nodules greater than or equal to 15 mm in diameter (n=40) developed areas of cystic degeneration, haemorrhage with cavitation ranging in diameter from 4 mm to 20 mm (Figure 9.01 & 9.02)). Of the tumours measuring 10 ± 1 mm in diameter, 7 showed no evidence of spontaneous necrosis on multiple sections while the remaining 3 showed a small foci of spontaneous haemorrhage within the tumour centre measuring approximately 2 mm in diameter. Cavitation was seen predominantly in large tumours (≥ 20 mm in diameter). The cavity was located centrally with relatively well defined edges and contained a haemorrhagic serosanguinous fluid. No tumour ulcerated spontaneously through the skin. The average diameter of spontaneous necrosis was 0.6, 6, 10 and 15 mm for the 10, 15, 20 and 30 mm diameter tumour cohorts respectively (Graph 9.2.2).

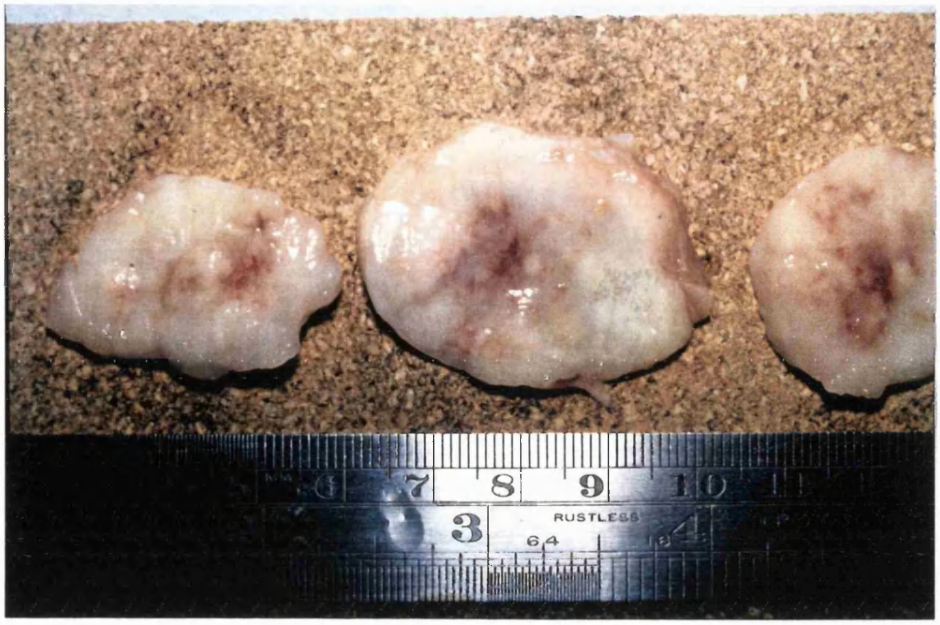
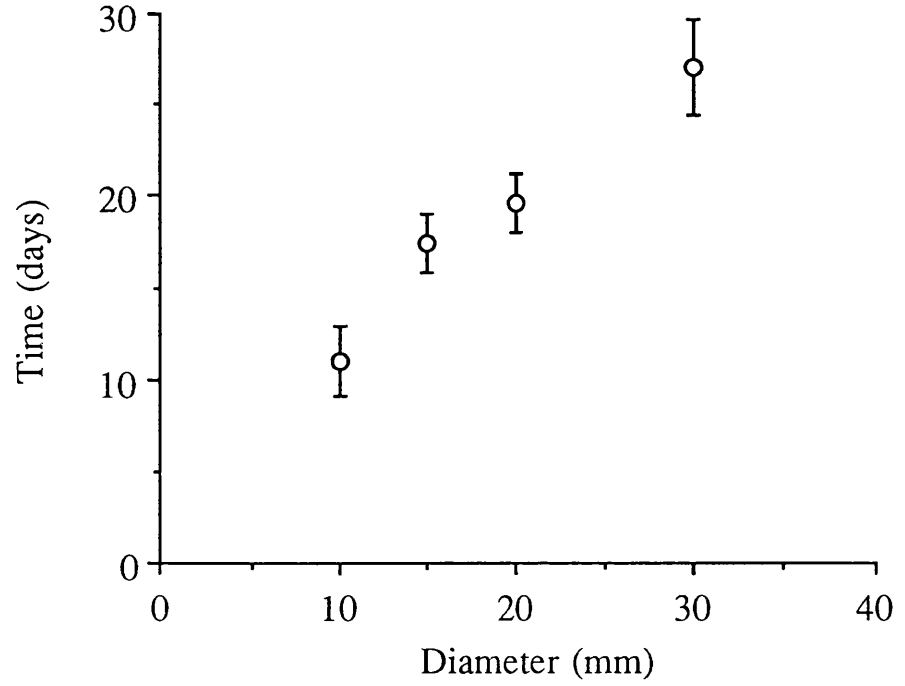
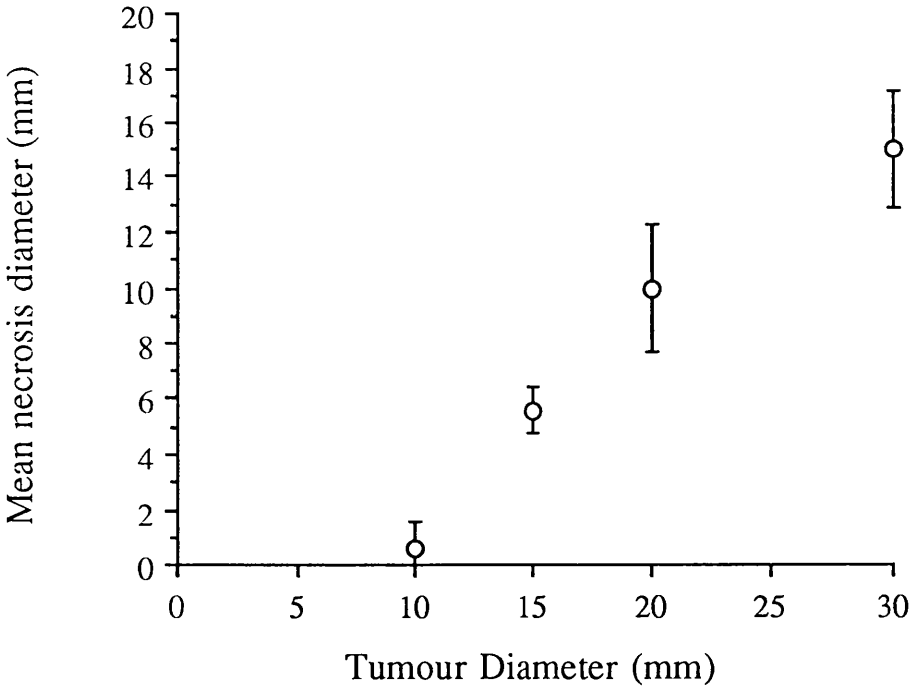


Figure 9.01. Naked eye appearance of sections across a 3 cm tumour. There are several areas of spontaneous haemorrhage.

Figure 9.02. Spontaneous central cavitation within a large transplanted tumour.



Graph 9.2.1. Interval in days (mean ± 1 standard deviation) from implantation to reach specified tumour diameter.



Graph 9.2.2. Relationship of spontaneous necrosis (mean ± 1 standard deviation) to tumour diameter.

9.2.4 CONCLUSIONS

Any tumour reaching or exceeding a diameter of 15 mm uniformly underwent spontaneous necrosis with or without cavitation of its centre. The larger the tumour the more extensive was spontaneous degeneration. This event was comparatively rare (30%) in the 10 mm diameter cohort and when it occurred, it consisted of a tiny foci of haemorrhage which is unlikely to influence laser tissue interaction adversely.

On the basis of these findings, a tumour diameter of 10 ± 1 mm was chosen for the remainder of the experiments.

9.3 LASER INDUCED TUMOUR NECROSIS : REPRODUCIBILITY AND VARIATION WITH TIME.

9.3.1 METHOD

The technique previously described for transplantation was performed in 25 adult CBH rats (140 to 250 gms). The tumours were allowed to reach a diameter of 10 ± 1 mm in their subcutaneous site in the right flank following which they were treated using ILH from a continuous wave Nd:YAG laser (model 212, CVI, Alburquerque, New Mexico, USA) Figure 9.03 & 9.04. This laser produces invisible infra red light at a wavelength of 1064 nanometers. A 500 microwatt helium-neon laser aligned co-axially with the Nd:YAG light provided a red visible aiming beam.

The animals were anaesthetised using intramuscular Fentanyl Citrate and Fluanisone (Hypnorm, Janssen Pharmaceuticals Ltd, Oxford, UK) at a dose of 0.05 ml / 100 gms. Using a 19 gauge hypodermic needle (external diameter 0.8 mm), the skin overlying the tumour was pierced and a 400 micron laser fibre coupled to the Nd:YAG laser passed into the tumour centre. A uniform diffuse glow throughout the tumour due to the helium-neon aiming beam confirmed a central position of the fibre tip. Each tumour was treated at a power of 2.0 watts applied for 500 seconds (1000 joules). Five animals were killed immediately following treatment (cohort A) while the remainder were caged separately receiving a standard diet ad libitum. Five animals were killed at intervals of 1 (cohort B), 3 (cohort C), 5 (cohort D) and 7 days from treatment (cohort E). All tumours

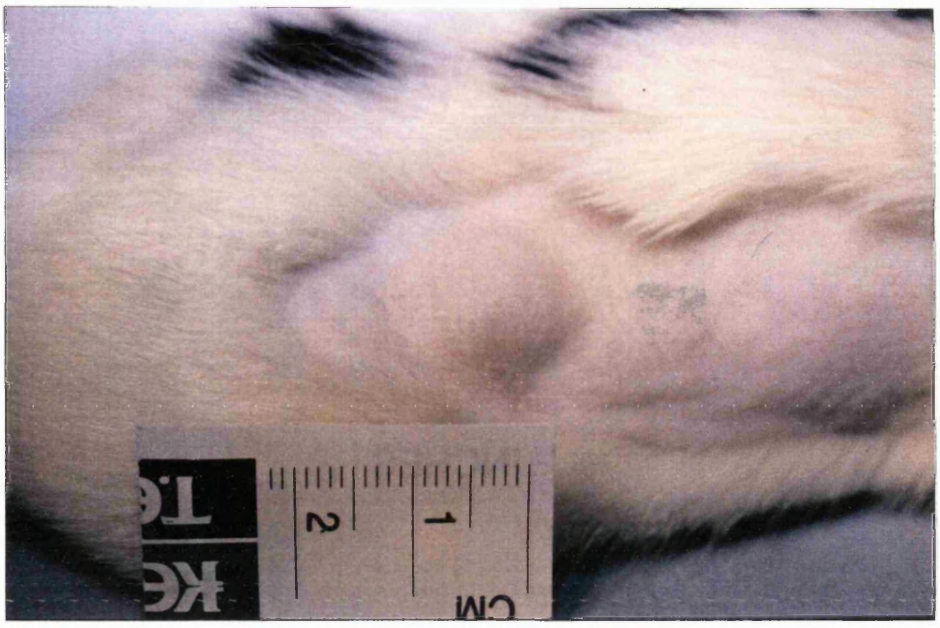


Figure 9.03. Eleven days from transplantation, there is a well defined 1 cm diameter subcutaneous tumour.

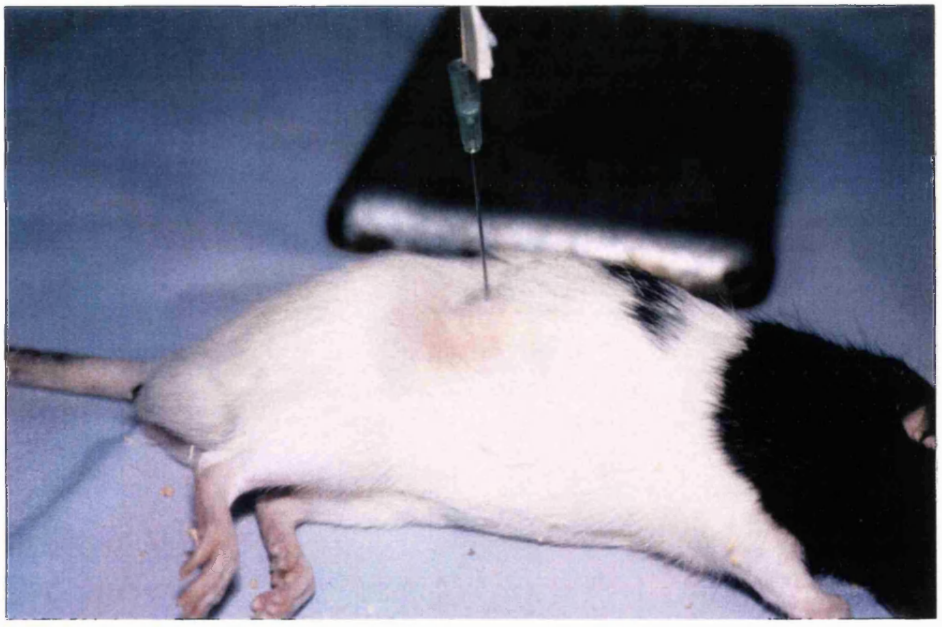


Figure 9.04. Needle and laser fibre in position within a tumour centre before laser treatment.

were excised in their entirety and submitted to a macroscopic and histological examination of the extent of laser mediated necrosis.

Statistical comparisons were made using Student's t test.

9.3.2 RESULTS

All tumours treated showed areas of coagulative necrosis which were roughly spherical in shape, well defined and centred around the fibre tip (Figure 9.05). There was very little or no charring around the fibre tip or within the tumours. Histological examination of Haematoxylin and Eosin (H&E) preparations of the treated tumours removed 3 days from treatment revealed a well defined central area of degenerative necrosis with clear demarcation between viable and non-viable tumour. Tumour cell nuclei were shrunken, very pale staining with a disorganised cytoplasm (Figure 9.06). There was little in the way of an acute cellular infiltrate around the treatment area. These features contrast markedly with histological changes seen in rat liver following ILH. For comparable laser parameters, the liver displays marked charring with cavitation surrounded by a well defined area of coagulative necrosis. An intense acute inflammtory response occurs around the degenerative zone with areas of suppuration and ingrowth of granulation tissue. Groups of multinucleate giant cells can occasionally be seen within the granulation tissue.

Cohort	*Animal 1*	*Animal 2*	*Animal 3*	*Animal 4*	*animal 5*
A (0)	*5x5x6*	*5x5x5*	*5x4x4*	*6x6x5*	*5x5x4*
B (1)	*7x7x5*	*8x7x6*	*7x7x7*	*8x7x6*	*7x7x6*
C (3)	*10x10x7*	*9x9x9*	*8x8x7*	*9x8x8*	*9x9x8*
D (5)	*10x7x9*	*10x10x8*	*10x8x7*	*9x9x9*	*9x8x7*
E (7)	*9x10x9*	*10x8x7*	*9x7x8*	*10x8x7*	*10x7x7*

Table 9.3.1. Necrosis dimensions in mm (± 1 mm) for each cohort. Figures in brackets in cohort column denote interval (days) from treatment.

The dimensions of the extent of necrosis for each cohort is given in Table 9.3.1. The average diameter of the extent of necrosis is 5, 6.9, 8.5, 8.7 and 8.4 mm for cohorts A, B, C, D and E respectively (Graph 9.3.1).

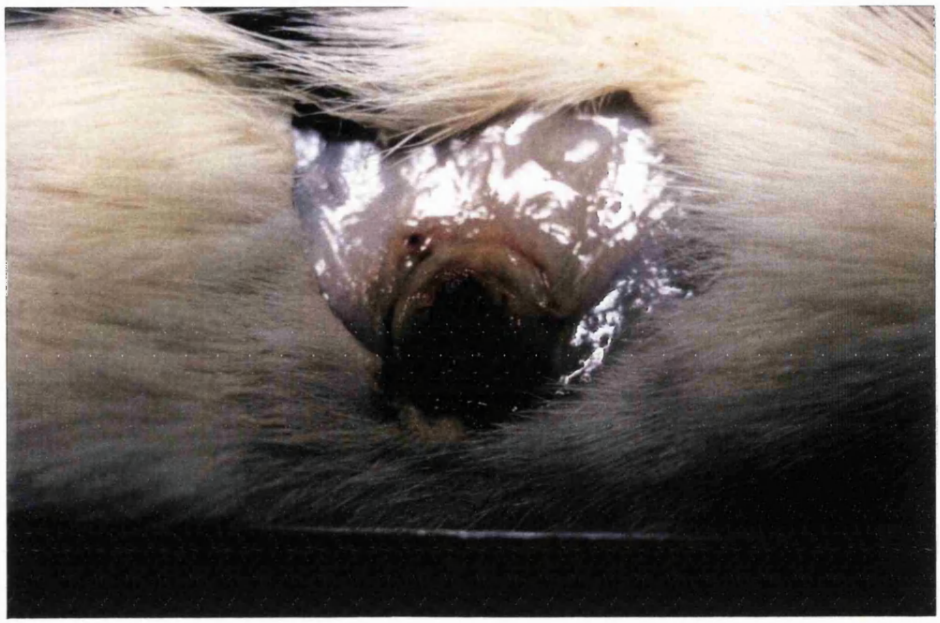


Figure 9.05. Transverse sections through a tumour 24 hours following treatment. There is a central zone of charring surrounded by coagulative necrosis. There is a thin rim of untreated tumour.

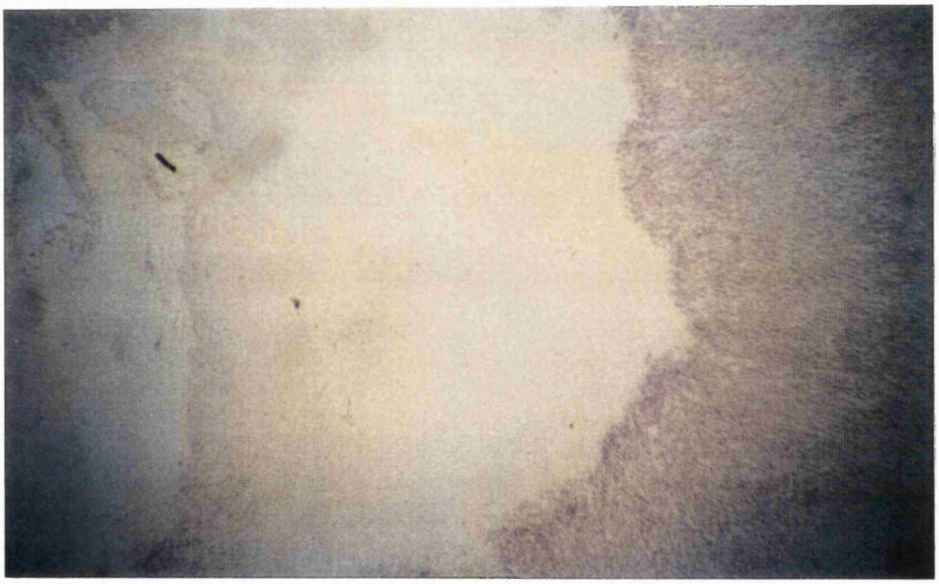
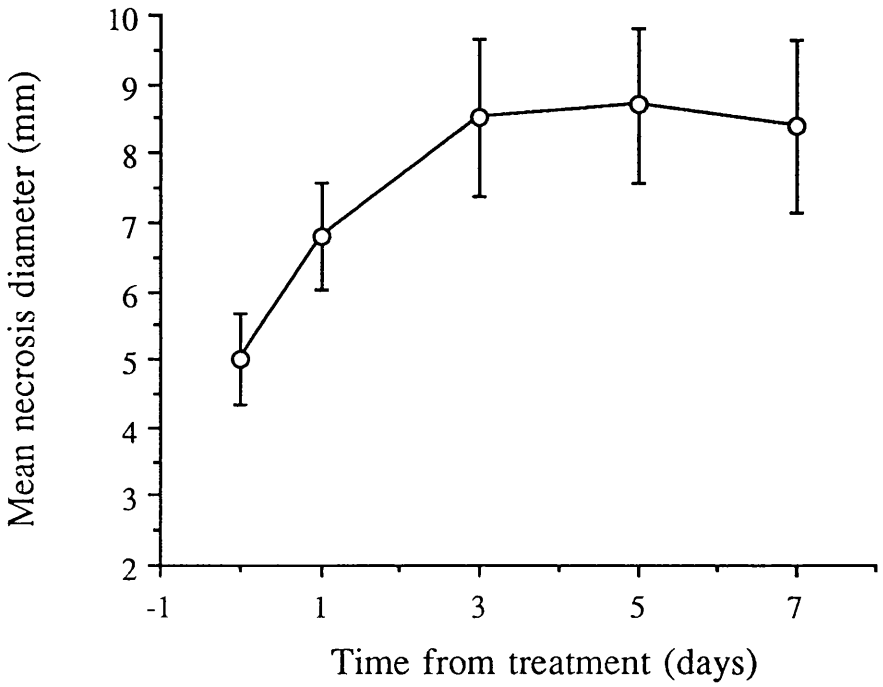


Figure 9.06. Low power histological appearance (H&E stain) 3 days following tumour treatment. There is a central zone of vacuolation with a well defined pale staining area of tumour necrosis. There is clear demarcation between viable and non-viable tumour.



Graph 9.3.1. Relationship of extent of laser induced necrosis (mean ± 1 standard deviation) to interval from treatment.

Given the errors in measuring the extent of necrosis (± 1mm) then from a practical point, the maximum extent of necrosis is representative from the third post treatment day. Statistical analysis confirms no significant difference at the 5% level between the average diameter of the extent of necrosis in cohorts C, D and E.

9.3.3 CONCLUSIONS

ILH produced well defined spherical areas of tumour necrosis the extent of which is maximal from the third post treatment day. The narrow error bars on graph 9.3.1 which consists of the mean ± 1 standard deviation would confirm the high degree of reproducibility of the extent of necrosis within each cohort.

In this tumour model, results suggest that fears concerning poor reproducibility of the biological effect due to possible heterogeneity in tumour structure would appear to be unfounded.

9.4 INTERSTITIAL LASER HYPERTHERMIA - INFLUENCE ON SURVIVAL.

9.4.1 METHOD

fifty adult CBH rats (150 to 250 mg) were transplanted with the Hosp 9AP6 mammary carcinoma in the right flank as previously described. The animals were closely observed. Once the tumours reached a diameter of 10 ± 1 mm, the animals were randomized into 6 treatment cohorts (n=42) and one control cohort (cohort A, n=8) Figure 9.03.

The animals were anaesthetised using intramuscular Fentanyl Citrate and Fluanisone (Hypnorm, Janssen Pharmaceuticals, Oxford, UK) at a dose of 0.05 ml / 100 gms. Using a similar technique to that described in section 9.2.2, a 400 micron laser fibre coupled to a continuous wave Nd:YAG laser was passed percutaneously into the tumour centre (Figure 9.07). All treatment cohorts were treated at a constant laser power of 2.0 watts which was applied for 200 seconds (cohort B, n=7), 300 seconds (cohort C, n=7), 400 seconds (cohort D, n=7), 500 seconds (cohort E, n=7), 700 seconds (cohort F, n=7) and 1000 seconds (cohort G, n=7).

Following treatment, all animals were caged separately receiving a standard laboratory diet ad libitum. The dimensions of residual or recurrent tumour and any ulceration following treatment was measured three times a week. From these dimensions, change in tumour volume was calculated assuming a roughly cylindrical pattern of growth. Any animal whose tumour reached or exceeded a diameter of 30 mm in any one plane was killed mercifully as such tumours interfered with the animal's mobility and threatened the viability of the overlying skin.

Cure was defined as 90 day survival from treatment with no evidence of local or distant tumour recurrence. Any animal surviving 90 days from treatment or dying before then with metastatic disease but without evidence of local tumour recurrence was defined as no sign of recurrence (NSR). All animals were subjected to autopsy. Histological sections of the treatment site and any recurrent or residual tumour were prepared using Haematoxylin & Eosin stains.

Statistical comparisons were made using Student's t test.

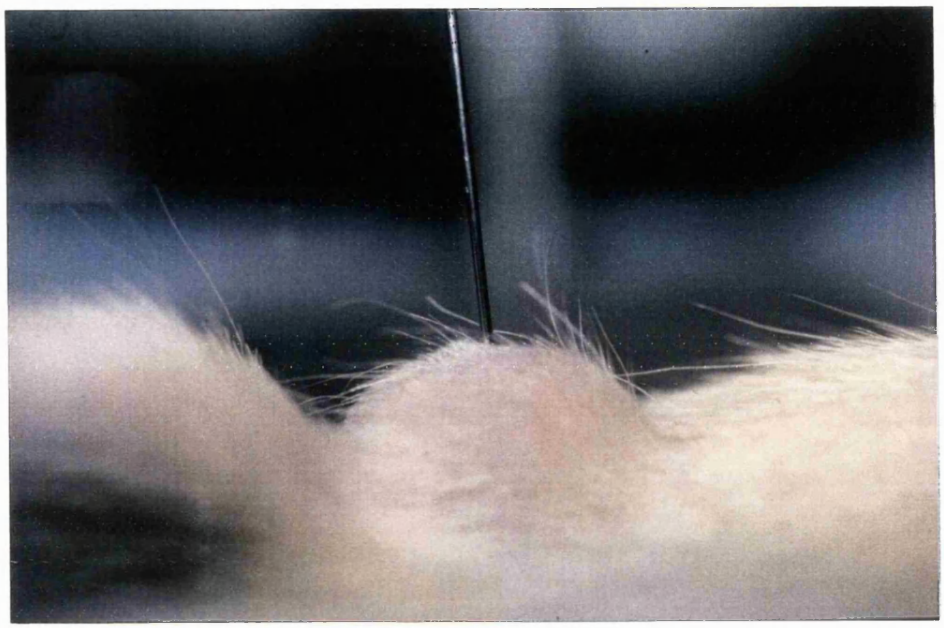


Figure 9.07. Close up view of percutaneous needle insertion into the tumour centre.

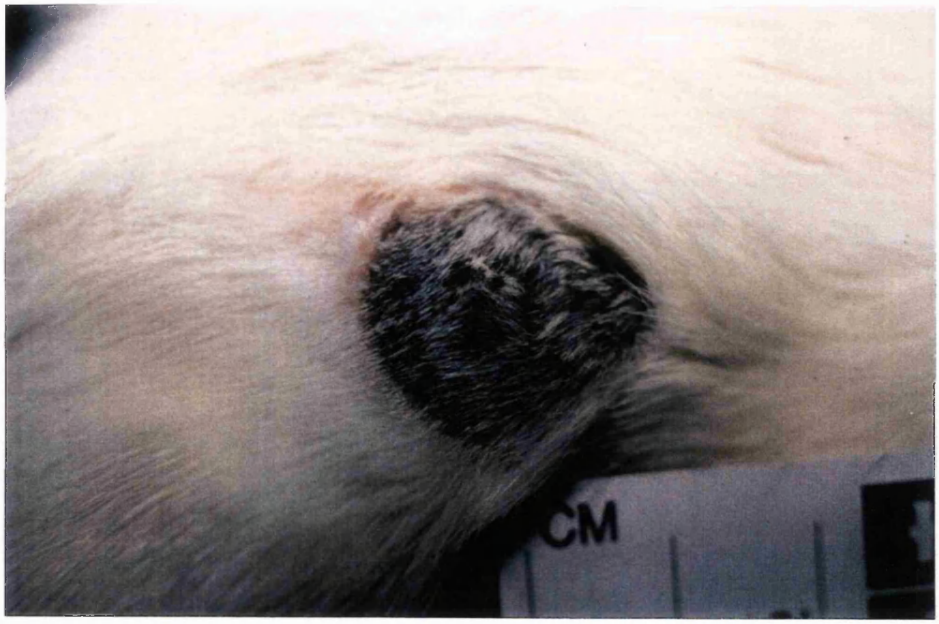


Figure 9.08. 48 hours following laser treatment, there is a well defined area of non-viable skin which will slough.

9.4.2 RESULTS

All tumours in the control group grew rapidly (Appendix VII). Animals satisfying the criteria for tumour size were killed 13 to 20 days (mean survival of 15 days) from the time the tumour had reached a diameter of 10 ± 1 mm. No animal in the control group developed spontaneous tumour ulceration.

All animals in the treatment cohorts showed evidence of at least partial tumour necrosis evident 5 to 7 days from treatment by necrosis with sloughing of the overlying skin to reveal an ulcer (Figure 9.08 & 9.09). Those animals without local recurrence gradually healed their ulcers completely by scarring within 6 weeks of treatment (Figure 9.10 & 9.11). The mean change in tumour volume (Graph 9.4.1) calculated 5 days from treatment was significantly lower in all the treatment cohorts compared to the control group ($p < 0.05$). Appendix VII and VIII document change in tumour volume in control and treatment cohorts 5 days from 10mm diameter and treatment respectively. Cohorts E to G did not show a significantly lower mean fall in tumour volume compared to the cohort D ($p > 0.05$).

The proportion of animals in each cohort showing tumour ulceration, complete loss of palpable tumour at some point from treatment, no sign of local recurrence and complete cures are shown in Table 9.4.1.

	Cohort A (Control)	*Cohort B (200S)*	*Cohort C (300S)*	*Cohort D (400S)*	*Cohort E (500S)*	*Cohort F (700S)*	*Cohort G (1000S)*
Ulcer	*0*	*7*	*7*	*7*	*7*	*7*	*7*
Loss of Tumour	*0*	*0*	*1*	*4*	*5*	*5*	*4*
NSR	*0*	*0*	*0*	*2*	*4*	*3*	*3*
Cures	*0*	*0*	*0*	*2*	*3*	*2*	*3*

Table 9.4.1. Proportion of animals in each cohort responding to treatment NSR = No Sign of Recurrence.

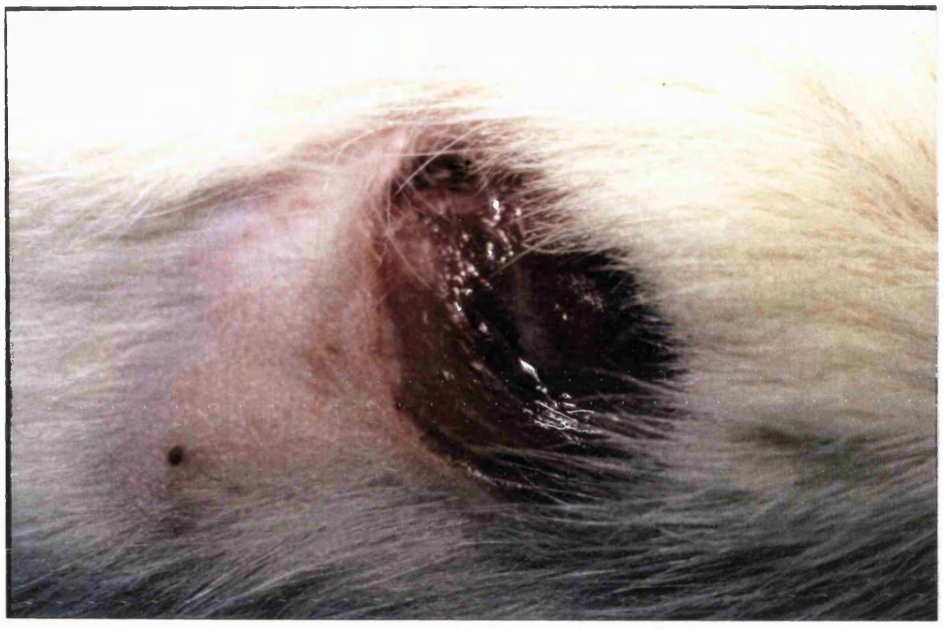


Figure 9.09. At 2 weeks from treatment, there is a well defined ulcer with no evidence of residual tumour.

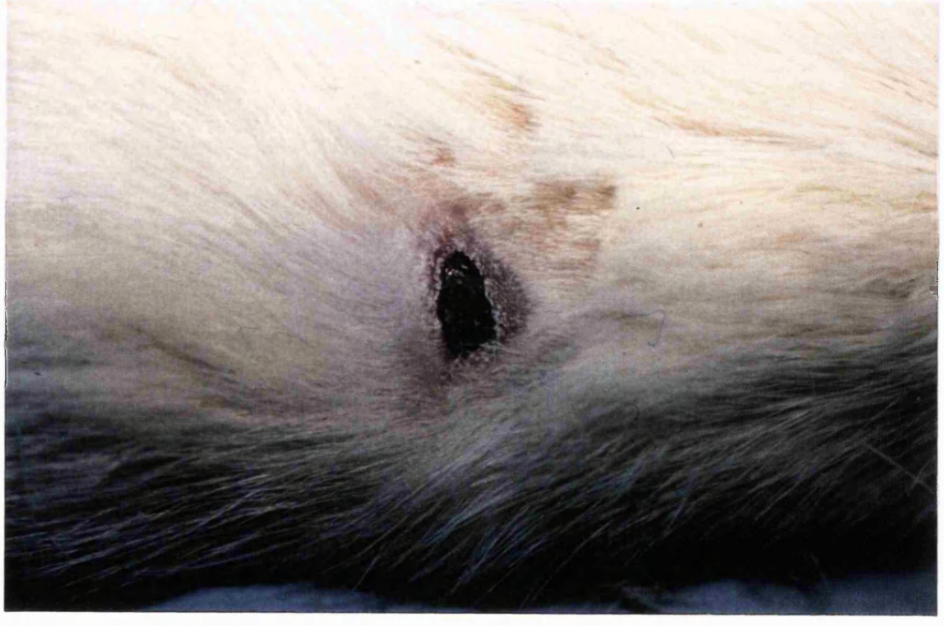
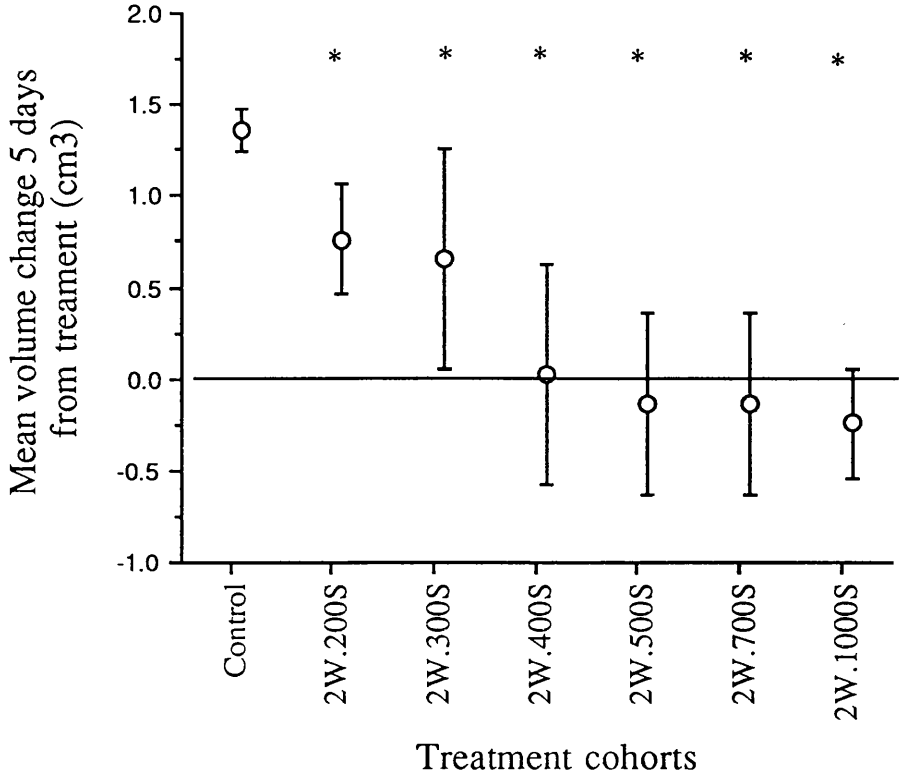
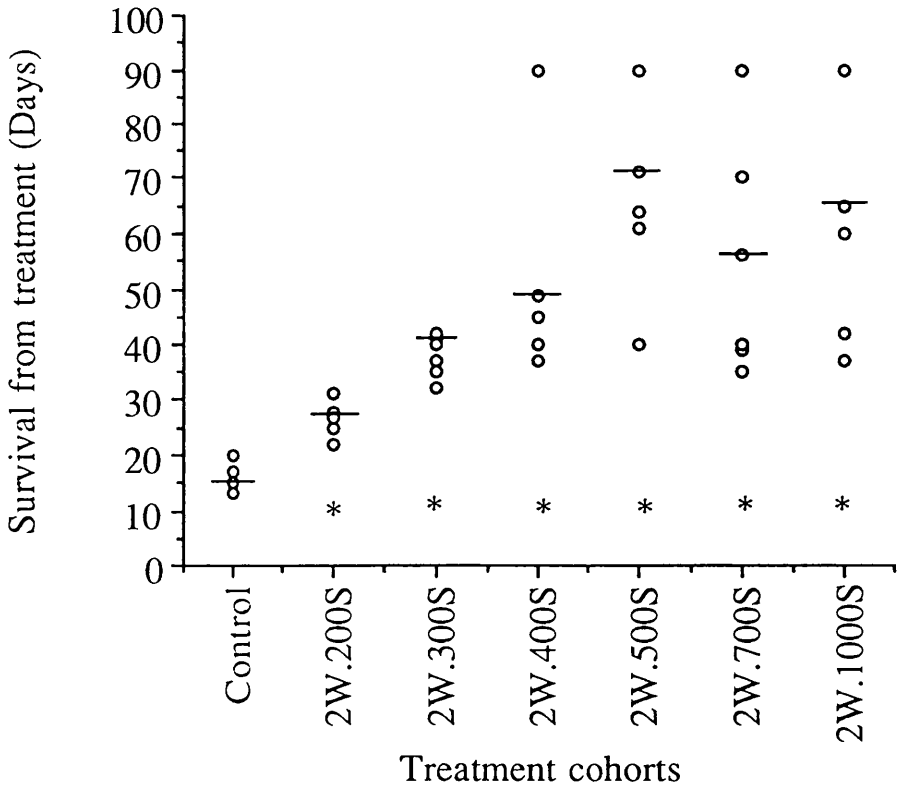


Figure 9.10. By 4 weeks, the ulcer has almost completely healed.



Graph 9.4.1. Tumour volume change (mean ± 1 SD) 5 days from laser treament.

*Significance values refer to comparison with control. * P < 0.05*



Graph 9.4.2. Survival times for each cohort. Horizontal bars denote median survival.

*Significance refers to comparison with control group. * p < 0.05*

Figure 9.11. At 6 weeks, a stellate scar remains as the only legacy of successful tumour eradication.

One animal in the cohort E and F died spontaneously at 71 and 70 days respectively from treatment with no evidence of local recurrence. Post mortem examination revealed pulmonary metastases in both animals.

Of the 11 animals surviving to 90 days from treatment, only one had local tumour recurrence measuring 5 mm in diameter. Cures were only achieved in the cohorts D to G. Survival from a diameter of 10 mm in the control cohort and from treatment in the remainder is shown in Graph 9.4.2. The horizontal bars denote median survival for each group. Survival is significantly prolonged in all treated cohorts compared to controls ($p < 0.05$). There is no significant survival benefit in cohorts E to G compared to cohort D ($p > 0.05$).

Appendix IX summaries survival for each animal in control and treatment cohorts. Table 9.4.2 shows the number of animals surviving at various intervals from tumour diameter of 10 mm in the control cohort and from treatment in the remainder.

Treatment	15 Days	30 Days	45 Days	60 Days	75 Days	90 Days
Cohort A (Control)	5	0	0	0	0	0
Cohort B (200S)	7	2	0	0	0	0
Cohort C (300S)	7	7	0	0	0	0
Cohort D (400S)	7	7	5	3	3	3 *
Cohort E (500S)	7	7	6	6	3	3 **
Cohort F (700S)	7	7	4	3	2	2 **
Cohort G (1000S)	7	7	5	5	3	3 **

Table 9.4.2. Proportion of animals surviving from treatment compared to control.

*** No sign of recurrence, * Recurrence in 1 out of 3 animals.*

Histological examination of the tumours removed within 24 hours of treatment showed a central area of degenerative necrosis which was well defined from surrounding viable tumour or normal tissues. There was little inflammatory response around the tumour. Nuclei in necrotic tumours were shrunken and extremely pale staining with a disorganised cytoplasm (Figure 9.06).

9.4.3 DISCUSSION

All treated tumours showed at least partial tumour necrosis. Once the appropriate laser parameters are defined and related to the tumour volume under treatment complete tumour regression with safe and complete healing could be produced in at least some animals.

Animals in all treatment cohorts showed significant reduction in mean tumour volume with prolonged survival compared to controls. Exposure times greater than 400 seconds at a constant power of 2.0 watts (800 joules) did not significantly reduce mean tumour volume or prolong median survival. The best results were obtained in the cohort treated for 500 seconds. Of 7 animals treated, 5 had complete loss of palpable tumour. There was no sign of local recurrence in 4 animals although 1 died from metastatic disease leaving 3 animals completely cured. In addition, animals in this cohort displayed a significantly longer median survival compared to the control group with a trend towards longer survival compared to all other treatment groups.

Previous work in normal rodent liver has shown that the extent of necrosis using the Nd:YAG laser plateaus at treatment energies greater than 600 to 1000 joules depending on the laser powers up to a maximum of 2.0 watts (Matthewson et al., 1987). Table 9.4.3 compares the mean necrosis diameter in liver and the subcutaneous tumours at comparable laser parameters 3 days following treatment. The maximum diameter necrosis measured in liver was approximately 15 mm compared to a value of 9 mm in subcutaneous tumour. It is possible that given a larger diameter tumour the maximum tumour necrosis may be even greater. However, even at lower comparable laser parameters, the extent of necrosis is significantly smaller in the subcutaneous tumour model.

LASER PARAMETERS	*HEPATIC NECROSIS DIAMETER (MM)*	*TUMOUR NECROSIS DIAMETER (MM)*
2 Watts.200 Seconds	*10*	*5*
2 Watts.300 Seconds	*16*	*7*
2 Watts.400 Seconds	*15*	*7*
2 Watts.500 Seconds	*15*	*9*

Table 9.4.3 - Comparison of mean maximum necrosis diameter in liver and subcutaneous tumour 3 days from treatment..

This disparity can be explained by the deep pigmentation of the liver causing extensive scattering of the forwardly transmitted laser light enhancing the extent of the biological effect as it interacts with a larger volume of tissue. It would seem that the scattering effect of hepatic tissue is more significant in enhancing laser tissue interaction than its abundant blood supply exerting a steal effect in reducing the thermal effect around the laser fibres.

To resolve this question more fully, the next logical step would be to transplant a tumour into the liver and treat it with the same laser parameters used in the mammary tumour. In this way, the relative effect of liver vascularity on the biological effect of ILH in tumour can be assessed more accurately.

CHAPTER 10. LASER DOPPLER FLOW MONITORING IN RODENT LIVER.

10.1 INTRODUCTION

The safe and effective application of ILH in oncology hinges on precisely matching the extent of laser mediated thermal necrosis to the volume of tumour under treatment. Interstitial fibre placement in tissues does not allow an accurate visual assessment of the result of treatment. At any rate, such an assessment is impractical when treating deeply seated organs such as the liver or pancreas. Thus tumour imaging and monitoring of the extent of necrosis are fundamental to the clinical application of ILH. The concepts of imaging and monitoring go hand in hand; their role in ILH can be divided into 4 key points.

1) Delineating accurately the limits of pathological tissue under consideration.

2) Establishing precisely whether the extent of laser mediated necrosis produced matches the tumour volume under treatment.

3) Following the process of resolution and healing at treated sites.

4) Detecting any signs of tumour recurrence at treated sites.

Radiological imaging techniques (US, CT or MRI) utilise physical properties of the tissues to produce a 2 dimensional representation of tissue topography. To a certain extent, there is an assumption that the extent of abnormal tissue is reflected exactly by the image seen. Monitoring can also be performed using the same radiological methods in real or near real time sequences. Changes in tissue physical properties as a result of thermal damage produce specific alteration in the character of the image produced. If the imaging modality has real time capability, for example US, then the evolving changes in the treated tissue can be followed. The extent of the changes in the treatment field can be controlled using an imaging window. In general, the whole of the treatment zone can be easily visualised. Regardless of the radiological technique used, for this approach to be successful, the nature and extent of changes visualised have to be correlated with the true extent of necrosis in treated tissue.

An alternative approach to monitoring is to use interstitial techniques assessing changes in pathophysiological parameters of tissues as a result of evolving thermal

changes. For example, changes in oxygen tension, temperature, blood flow or transmission of laser light. Compared to their radiological counterparts, these techniques are relatively invasive requiring a sensing probe to be placed at some specific point of interest in the treatment zone. By their nature, information can only be provided at the probe site sampled which may give rise to sampling errors. This can be minimised by using several probes although there must be a practical limit on the absolute number used. When treating deeply seated organs, probe placement brings with it specific problems. Probe dimensions must be such to allow safe percutaneous insertion and must not interfere with treatment. In addition, they must be cost effective, simple to use providing reproducible results. To be most effective, probes will require precise placement under radiological control. From these considerations, it seems likely that the role of invasive monitoring alone is limited, although they may have a complimentary role when combined with conventional radiological imaging.

In this thesis, ultrasound has been used extensively for imaging and monitoring. It is easy to use, non invasive, portable, relatively cheap, possesses a real time capability and since it does not use ionising radiation, it can be used in any room without safety modifications. Experimental work has confirmed its usefulness for relatively accurate percutaneous fibre placement while the significance of real time changes in normal liver have been well studied by several authors (Steger et al; 1992, Dachman et al; 1990, Bosman et al; 1991). Drawbacks include a resolution limit on the diameter of lesions that can be reliably detected in the liver ($\leq$ 2 cm) and high dependancy on the experience and skill of the operator. Real time sonographic changes seen in treatment of liver metastases are similar to those observed in experimental work treating normal canine liver. However, experimental data from chapter 9 have demonstrated smaller areas of necrosis in hepatic metastases compared to normal liver for comparable laser parameters. Differences in the optical characteristics of normal liver and tumour is likely to be the reason for this. It is therefore debatable whether real time US changes in normal liver can be reliably extrapolated to hepatic tumours.

Relative to CT and MRI, the resolution of US in the liver leaves some room for improvement. This is particularly noticeable when trying to determine the junction of

necrotic and viable tissue following treatment of metastases. The edge of the hyperechogenic zone maybe indistinct due to distortion of the US image by hyperechogenic signal arising from previously treated sites. This makes it difficult to be confident on the completeness of a treatment. While CT and MRI may represent one way forward, as yet, there has been no study evaluating their real time performance during ILH treatment and secondly, the relationship of such changes as markers of reversible and irreversible tissue changes have not been evaluated. The potential disadvantages of CT and MRI is that they are expensive in their most sophisticated guise which is likely to be required for rapid sequential scanning. This is necessary to provide dynamic imaging of the evolving changes. An alternative is to combine an interstitial monitoring technique with US.

While no complete description exists of the pathophysiological changes that occur to tissue following hyperthermia, vascular shutdown with a secondary ischaemic effect is undoubtedly an important contributing factor. It is thought that protein denaturing and contraction with further tissue shrinkage due to dehydration produce a reduction in vessel luminal diameter. As a result, a state of relative vascular stasis allows endothelial damage to occur with coagulation of luminal blood. This has been verified by Matthewson and his colleagues (1987) who injected a radio-opaque polymer in the the arterial tree of a rat liver following low power photocoagulation. They demonstrated total loss of the vascular pattern in an area corresponding to the necrotic zone. It would seem logical that a simple technique to assess changes in blood flow at the treatment site during photocoagulation may be a useful way to evaluate tissue viability.

There are several ways of assessing tissue perfusion, each having specific advantages and disadvantages. These will be considered briefly :-

I) CLINICAL TEST - Assessment of tissue colour and temperature are indirectly related to blood flow. However, interpretation is difficult as they are influenced by environmental factors. For deeply seated organs with no visual access, these methods are clearly impractical.

II) CHEMICAL METHODS - Fluorescein solution van be injected directly into the circulation of the organ under treatment and the tissue visualised under ultraviolet light. The interval between injection to maximum visualisation is a measure of blood flow. This technique is

invasive, non continuous and provides no quantitative measure of flow. Visualisation of the treated tissues is mandatory.

III) RADIO-ISOTOPE METHOD - The clearance of various isotopes such as Sodium 24, Iodine 131, Technetium 99 an Xenon 133 give a quantitative but non continuous measure of blood perfusion. This technique is useful in assessing flow in compartments and individual organs but is too insensitive for measuring flow in small tissue volume within well vascularized organs such as the liver.

IV) INSTRUMENTAL METHODS - Thermocouples are inexpensive and easy to handle. The relationship between temperature and tissue necrosis is however imperfectly understood. Alternatively, optical techniques can be used to assess tissue perfusion in one of two ways. Microscopic techniques (Fagrell, 1984) and those methods where blood flow is determined by the way light interacts with tissue under study. Stern (1975) proposed using monochromatic light to determine blood perfusion. The amplitude and frequency of the waves are changed when scattered by moving cells in the microcirculation. The change in amplitude is related to the number of red cells while the difference in frequency between the incident monochromatic laser light and the frequency shifted back scattered light is known as the doppler shift and is proportional to the velocity of the blood cells. This forms the basis for laser doppler flow monitoring of the microcirculation. The microcirculation refers to blood flow through smaller blood vessels such as capillaries, arteriolles and venules. Each type of these small vessels has its own characteristic function and structure while each organ has its own characteristic microcirculatory bed with differences in vascular architecture and innervation.

The work described in this chapter assesses the feasibility of using laser doppler flowmetery (LDF) as a real time monitor modality of the extent of necrosis produced using low power ILH from a Nd:YAG laser in rodent liver. It has been shown by Lui and his colleagues (1991) that the blood flow in the hepatic microcirculation of rats as assessed by LDF falls significantly following occlusion of the portal vein and hepatic artery. This demonstrates the potential of LDF for registering changes in hepatic microcirculation following different therapeutic manoeuvres.

Preliminary general consideration of laser doppler flowmetery and the practicalities of its use will now be discussed.

10.2 LASER LIGHT SCATTERING IN TISSUE

Electromagnetic radiation interacts with tissue in two principle ways : absorption and scattering. Absorption causes the photon energy to be converted to heat. Scattering is a directional change caused by electro-magnetic interaction with matter. Depending upon the refractive index and the scatterer size, different scattering phenomena take place.

Rayleigh scattering occurs if the scatterer is a much smaller dimension than the wavelength of the incident radiation. The scattering is then isotropic, that is having the same physical properties in all directions. Photons scattered by large particles is called Mie scattering and tends to be highly forward directed. This results in a significantly lower average frequency shift of the light compared with back scattering.

Laser doppler flowmetery utilises a Helium-neon laser at a wavelength of 632.8 nanometers (red light). Red cells are an irregular structure an order of magnitude larger than the wavelength of red light, thus a large proportion of light is scattered in a forward direction. In tissues with high blood flow, the incident light beam is likely to undergo scattering from more than one moving cell resulting in successive doppler shifts. This phenomenon is known as multiple scattering or doppler broadening.

10.3 LASER DOPPLER FLOWMETER

Laser doppler flowmetery (LDF) is a relatively non invasive method capable of real time measurement of the microcirculation. A collimated beam of monochromatic light generated by a low power laser (Helium-Neon, wavelength 632.8 nm at an output power of 2 milliwatts) is carried to the tissue under study using an afferent fibre optic. The light is diffusely scattered and partly absorbed within the irradiated tissue volume. Light hitting moving cells will undergo a doppler shift with a change in frequency while that component hitting stationary structures will be unchanged. The magnitude and frequency shift are directly related to the number and velocity of red cells but virtually unrelated to the direction in which they move. The measurement probe incorporates 2 additional fibres

which pick up and carry back part of the illuminated beam back scattered to photodetectors where it is converted into electronic signals. The back scattered light consists of a mixture of doppler shifted and non doppler shifted wavelengths. The former is extracted from the laser noise and other interfering frequencies with effective suppression of the background noise to produce a cell motion correlated signal called the flux. This is defined as the product of the number of blood cells moving in the measured volume and the mean velocity of these cells.

The instrument used in the experiments described in the next section of this chapter is a Perimed PF3 laser doppler flowmeter (Perimed, Sweden) figure 10.01. It uses a Siemens LGR 7621S helium-neon laser producing laser light at a wavelength of 632.8 nanometers at a power of 2 milliwatts coupled to a PF302 needle probe (figure 10.02). The probe dimensions are 53 mm long with an external diameter of 0.45 mm. The general operating characteristics of this instrument will now be considered.

10.4 GENERAL OPERATING CHARACTERISTICS

The penetration depth of radiation is the depth from the measuring surface at which light intensity decreases to about 37% of its surface value. In Caucasian skin at 632.8 nm this distance is about 0.6 mm. This value is governed by the absorption properties of an organ which depends upon the haematocrit (blood content), percentage oxygenation and pigmentation. In liver which has pronounced absorption properties, the penetration depth is likely to be less than 0.6 mm.

Red cells form the dominant contribution to movement relative to the instrument probe but there are smaller components from leucocytes and thrombocytes proportional to their component of blood flow. These components do not disturb the the reading because they form part of the blood flow. There is an insignificant contribution which is not flow related from muscle cells, vessel walls and various membranes. It is these which account for non zero on complete inflow occlusion of an organ. The influence of large vessels in the sampling volume is small as the wall is too thick to allow more than a limited amount of light in and out. As to be expected, all measurements must be conducted at well controlled room temperatures.

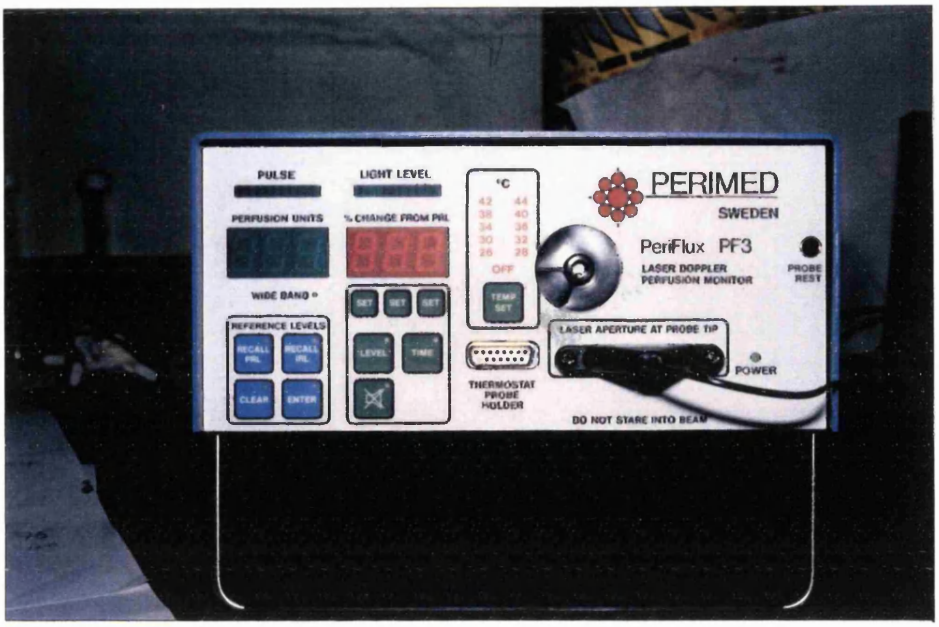


Figure 10.01. A perimed PF3 laser doppler flow meter.

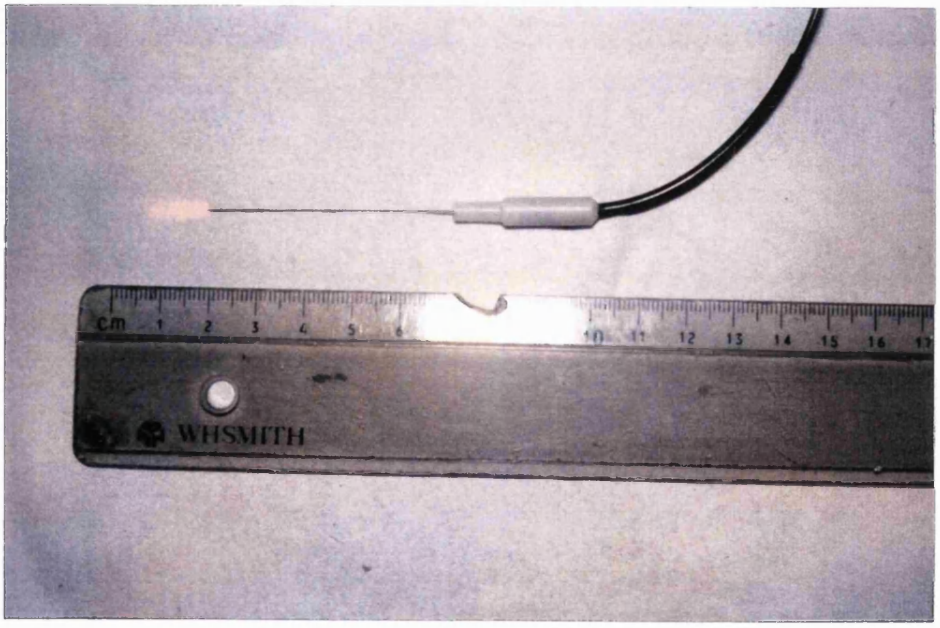


Figure 10.02. A PF 302 needle probe with an external diameter of 0.45 mm.

10.4.1 WIDE BAND INDICATOR

For technical reasons, it is necessary to limit the frequency range which the periflux is sensitive to doppler shift . This is set at 20 Hz to 4 KHz. In high perfusion organs such as the liver, it is possible to increase the upper doppler frequency limit from 4 KHz to 20 KHz. This frequency range is sufficiently large to encompass all doppler frequencies that may occur in clinical use.

10.4.2 PRACTICAL SIGNIFICANCE OF LINEARITY

Cell perfusion is given by the product of the number of blood cells and their mean velocity. It is possible to produce changes in cell perfusion by changes in the number of red cells at a constant velocity or changes in red cell velocity at a constant concentration. In practice, both will change simultaneously, although in the microvascular circulation it seems variations are more often caused by changes in cell concentration at a more or less constant velocity.

Measuring perfusion reaction to a stimuli such as ILH in terms of the baseline perfusion then the linear characteristics of the PF3 allow a meaningful relative measure to be made. Organs such as the liver having high blood cell concentration produce multiple doppler shifts of the incident light. In addition to mixing between unshifted light and light shifted by one single reflection, there will be false doppler signals created by light undergoing several doppler shifts resulting in under estimation of perfusion. However, the linear characteristics of the PF3 eliminates this problem by using a conversion factor related to the total photocurrent power, fluctuation power and the doppler shifted fraction of the photocurrent.

10.4.3 PERIFLUX ZERO

Before every experiment, the zero was established by placing the probe against an object where no movement occurred. Backscattered but non-doppler shifted light was produced corresponding to a perfusion display of zero. This setting is stable and independent of variation in the laser intensity, tissue pigmentation and reflectance.

Occasionally minor adjustment of the zero was necessary by altering the zero potentiometer at the rear panel of the instrument.

10.4.4 PERIFLUX CALIBRATION

This is performed using a PF 100 motility standard and the PF 3 in the wide band mode. The standard consists of 2.5 cm^3 of colloid suspension of latex particles whose Brownian motions is used as a motility standard. At standard temperature, 22°C, the motility standard produces a reading of 250 perfusion units (PU) ± 5%. With the motility standard in the same room, the PF3 was turned on for 30 minutes allowing it to reach its working temperature. With the wide band mode on and the time constant to medium (0.25 seconds), the PF 302 needle probe was held rigidly within the motility standard. The gain potentiometer was adjusted until a periflux reading of 250 ± 15 PU was obtained.

10.4.5 MOVEMENT AND THE MOVEMENT ARTEFACT FILTER

All laser doppler flowmeters employ flexible optical fibres for signal transmission and are afflicted by movement artefacts due to movement of the probe relative to the tissues and visa versa. The PF3 incorporates a new double channel probe which movement artefacts are significantly reduced in combination with a movement artefact filter.

The movement artefact filter consists of an electronic circuit that can be switched into the signal line. Its main component is a slew rate filter sensitive to rate of change of the perfusion signal. A rate of change in signal faster than a predetermined limit rate which exceeds the steepest slope rate seen in physiological systems triggers the slew filter which locks the periflux reading to that value prior to commencement of the disturbance.

SECTION 1

10.5 BASELINE ASSESSMENT OF RODENT LIVER MICROCIRCULATION

Each organ has has its own microcirculatory bed with differences in vascular architecture and innervation. The first section describes the characteristics of rodent liver microcirculation by determining spatial and temporal variations in flux values. It is known that LDF is sensitive to movement artefacts despite a movement artefact filter. Given the

respiratory excursions of the liver particularly in small animals with high metabolic rates, then it is important to assess the reproducibility of flux measurements at a given site. Temporal, spatial variation and flux measurement reproducibility are assessed in section one. The second section describes experimental work to assess the feasibility of using LDF in real time to assess the extent of laser mediated necrosis during low power photocoagulation.

All experiments were performed using a PF3 laser doppler flowmeter (Perimed, Sweden) coupled to a PF 302 needle probe (Figure 10.01 & 10.02). The PF3 was turned on and allowed to warm up for at least 30 minutes prior to use. The instrument was set in the wide band mode to respond to doppler shifts in the range of 20 Hz to 4 KHz with a medium flux time constant (0.25 seconds) and the movement artefact filter in operation.

The probe was placed on the liver surface in preference to interstitial placement. Due to probe calibre, interstitial placement invariably produced bleeding from the liver parenchyma. This never threatened the wellbeing of the animals but was sufficient to attenuate laser light transmission through the tissues leading to loss of the doppler signal or producing falsely low flux values. Experimental work (Lui et al; 1991) in normal rodent liver has shown no significant variation in flux values derived from surface and interstitial placement.

10.5.1 METHOD

Fourteen adult male wistar rats (200 to 350 gms) were anaesthetised using intra-muscular Fentanyl citrate and fluanisone (Hypnorm, Janssen Pharmaceutical, Oxford, UK) at a dose of 0.1 ml per 100 gms body weight. The liver was exposed at laparotomy through a midline incision and the left lobe mobilised and delivered into the wound to be placed on a moistened guaze swab resting on the anterior abdominal wall. During the experiments, the liver was periodically irrigated with normal saline at body temperature to prevent excessive drying and ensure good coupling between the liver surface and the LDF probe.

The PF302 probe was placed on the liver surface with just sufficient pressure to obtain a steady reading and yet without occluding the microcirculation or piercing the liver capsule. Once satisfactory, the probe position was secured in a clamp (Figure 10.03). This

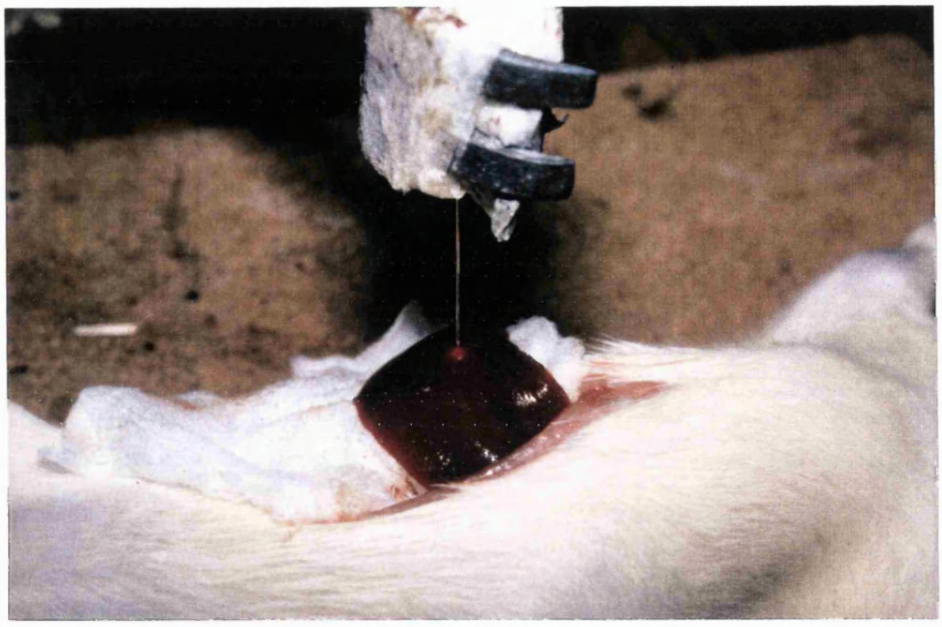


Figure 10.03. The left hepatic lobe delivered through the wound at laparotomy. The PF 302 probe rests on the surface.

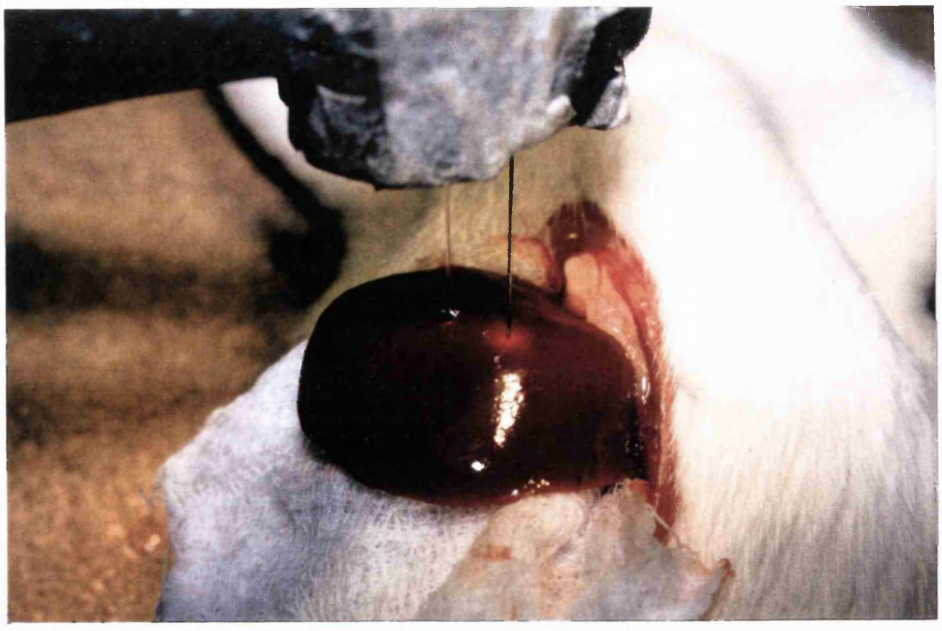


Figure 10.04. Needle probe and laser fibre in position during photocoagulation of the left lobe.

was not always easy to achieve due to marked respiratory excursions of the liver. Heavy sedation of the animal kept such excursions to an acceptable level.

10.5.2 REPRODUCIBILITY

Two Wistar rats were prepared in the manner described above. The needle probe was positioned at four different sites on the left liver lobe in each animal giving a total number of 8 sites. A steady state reading was taken after 60 seconds at each probe site. This was repeated 10 times at each probe site giving a total of 80 values.

10.5.2.1 RESULTS

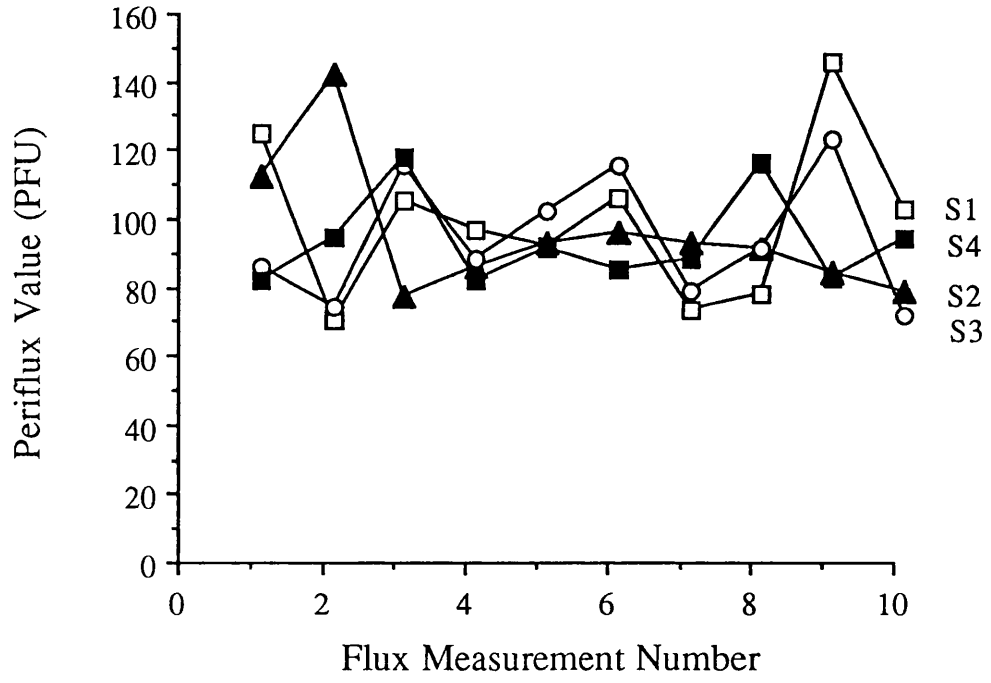
The flux readings for each placement in both animals are tabulated in Table 10.5.1. Sites 1 to 4 (S1-S4) were taken from the first animal while sites 5 to 8 (S5-S8) were from the second.

	ANIMAL 1				*ANIMAL 2*			
FLUX NO.	*S1*	*S2*	*S3*	*S4*	*S5*	*S6*	*S7*	*S8*
1	*122*	*109*	*83*	*79 **	*100*	*89*	*130*	*110*
2	*67 **	*139 †*	*71*	*91*	*89*	*99*	*99*	*109*
3	*102*	*74 **	*112*	*115 †*	*102*	*117*	*109*	*89*
4	*94*	*83*	*85*	*79 **	*133 †*	*88*	*85 **	*78 **
5	*89*	*90*	*99*	*88*	*120*	*94*	*93*	*98*
6	*103*	*93*	*112*	*82*	*97*	*126 †*	*100*	*115*
7	*70*	*90*	*76*	*85*	*77 **	*99*	*117*	*121 †*
8	*75*	*88*	*88*	*113*	*99*	*86 **	*114*	*79*
9	*143 †*	*81*	*120 †*	*80*	*107*	*95*	*144 †*	*82*
10	*100*	*76*	*69 **	*91*	*119*	*96*	*111*	*97*
MEAN	*97*	*92*	*92*	*90*	*104*	*99*	*110*	*97*
%	*78*	*71*	*55*	*40*	*54*	*40*	*53*	*44*

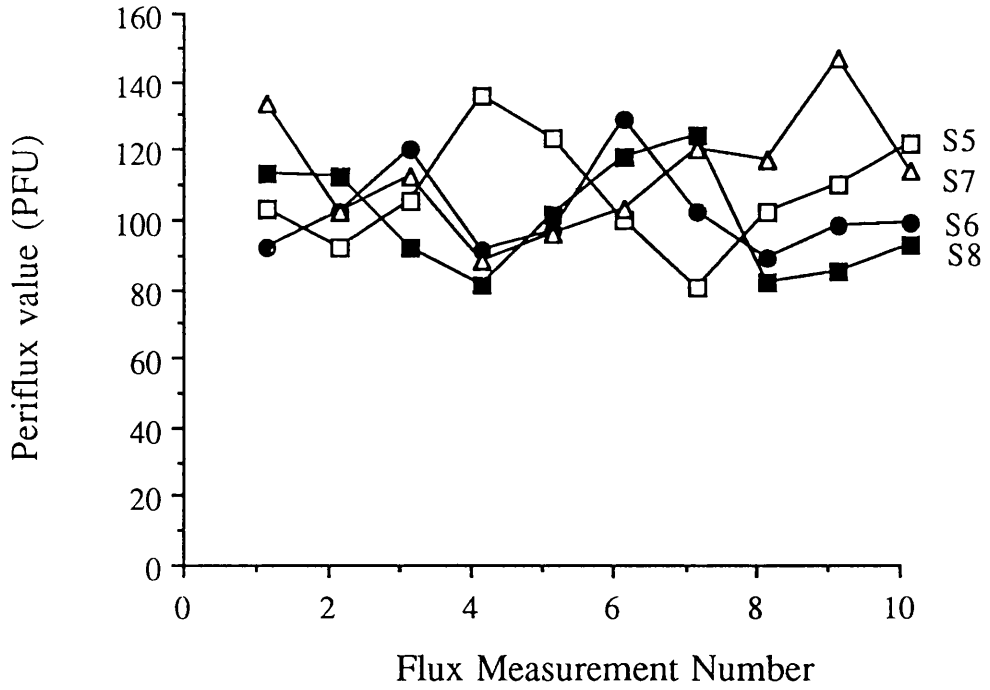
Table 10.5.1. Eighty flux values recorded at 8 sites with 10 values recorded at each site.

*† - Maximum Flux * - Minimum Flux*

The mean flux value was been calculated for each site. The difference between the maximum (†) and minimum flux (*) at any given site was calculated as a percentage of the



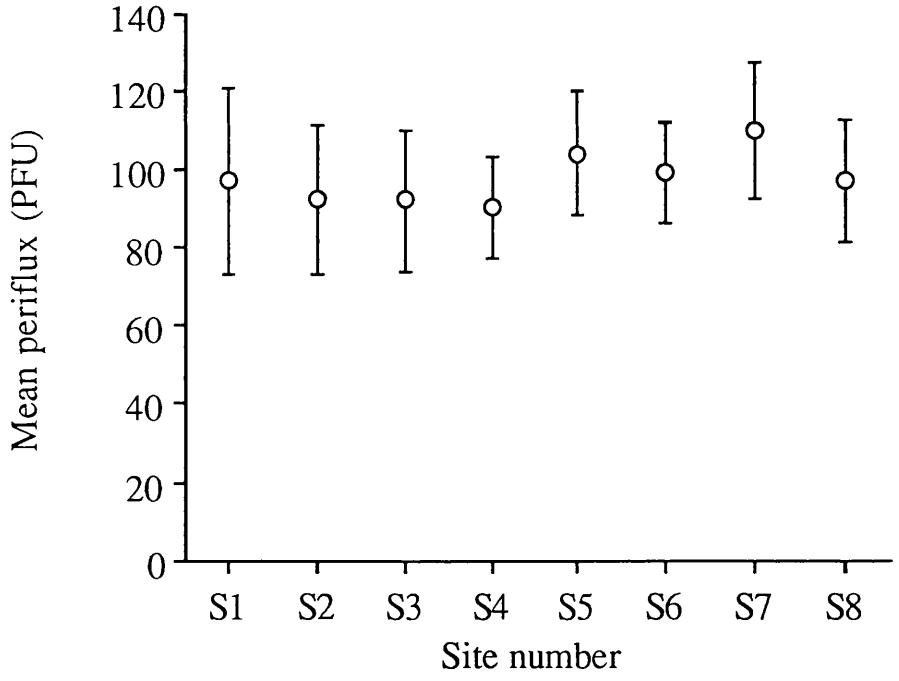
Graph 10.5.1. Flux variation at 4 different sites (S1-S4) in animal 1. Ten flux measurements were obtained at each site.



Graph 10.5.2. Flux variation at 4 different sites (S5-S8) in animal 2. Ten flux measurements were obtained at each site.

mean. The maximum variation was 78% of the mean at site 1 with a minimum of 40% of the mean at sites 4 and 6. Of the 8 sites evaluated, the percentage variation between the maximum and minimum flux was less than 75% of the mean in 7 and less than 50% of the mean in 3. Graph 10.5.1 and 10.5.2 demonstrate how relatively little the flux varied over the 10 readings obtained at each of the 4 sites in animal 1 and 2 respectively. This suggests that there is good reproducibility of flux measurement at each site.

Any variation seen is most likely to be due to differences in probe pressure exerted on the liver surface. The mean flux of 10 readings at each of the 8 sites were remarkably similar and are illustrated in Graph 10.5.3. The error bars represent the mean flux plus or minus one standard deviation. The narrow error bars suggest that flux values at any given site are relatively well reproduced.



Graph 10.5.3. Comparison of mean flux (± 1 SD) at each of the 8 sites in both animals. Each point is the mean of 10 values at each site.

10.5.3 SPATIAL VARIATION

Eight Wistar rats were prepared in the manner described above. The needle probe was positioned at 10 different sites on the left lobe in each animal. A steady state reading was taken from each site 60 seconds from placement. A total of 80 values were obtained.

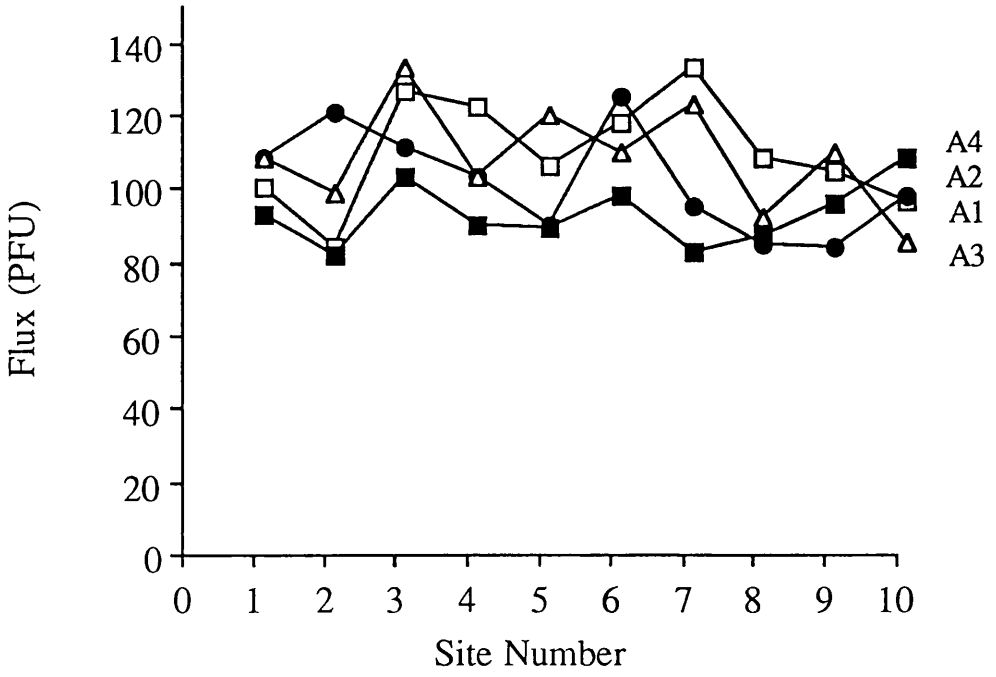
10.5.3.1 RESULTS

The Flux values at each of the 10 sites in each animal (A1-8) are shown in table 10.5.2. The mean flux for each animal was calculated. The difference between maximum (†) and Minimum (*) flux for each animal is then calculated as a percentage of the mean. The maximum variation was 58% of the mean in animal 6 with the lowest difference of 29% of the mean in animal 4. The variation between maximum and minimum flux values was less than 50% of the mean in 6 animals with the remaining 2 recording a difference of 56 and 58% of the mean. Graphs 10.5.4 (animals 1 to 4) and 10.5.4 (animals 5 to 8) demonstrate the variation in flux at the 10 different sites. Regardless of site in each animal, they show reasonably consistent flux values. Therefore, there seems to be no strong spatial influence on flux value within any given animal. Graph 10.5.6 illustrates the relationship of mean flux (average of 10 readings in each animal) in all 8 animals. The error bars represent the mean plus or minus one standard deviation. The mean values are comparable. The spread of error bars is relatively small and comparable in all animals.

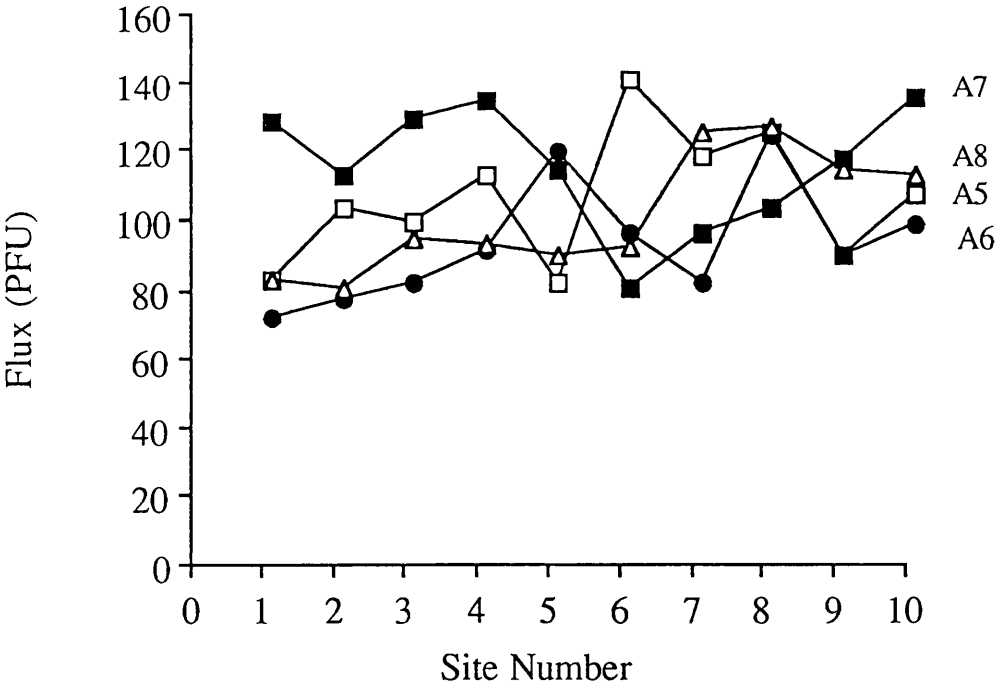
SITE	A1	A2	A3	A4	A5	A6	A7	A8
1	97	105	105	90	80	69 *	125	80
2	81 *	118	96	79 *	100	74	109	77 *
3	124	108	130 †	100	96	79	126	91
4	119	100	100	87	109	88	131	90
5	103	87	117	86	79 *	116	111	87
6	115	122 †	107	95	137 †	93	77 *	89
7	130 †	92	120	80	115	79	93	122
8	105	82	89	84	122	121 †	100	123 †
9	102	81 *	107	93	87	87	114	111
10	94	95	83 *	105 †	104	95	132 †	109
MEAN	107	99	105	90	103	90	112	98
%	46	41	45	29	56	58	49	47

TABLE 10.5.2. Eighty flux values recorded from 10 sites in each of 8 animal (A1 to A8)

*† - Maximum flux * - Minimum Flux*

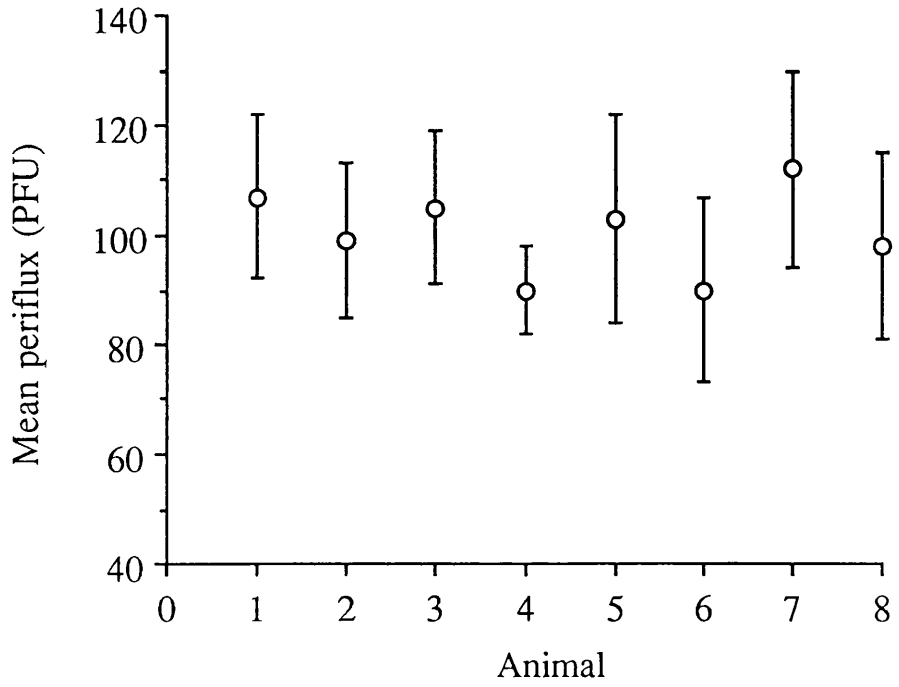


Graph 10.5.4. Variation of flux with site in Animals (A) 1 to 4.



Graph. 10.5.5. Variation of flux with site in animals (A) 5 to 8.

Generally, there would appear to be little variation in the flux values between any of the 8 animals. Any differences could be attributable to differences in probe pressure, respiratory excursion and level of sedation.



Graph 10.5.6. Comparison of mean flux (± 1 SD) in all 8 animals. Each point represents the mean flux of values at10 sites .

10.5.4 TEMPORAL VARIATION

In two suitably prepared animals, the needle probe was placed at two sites in the centre of the left lobe in each animal. A reading was taken at 5 second intervals for 60 seconds giving 12 values per site. This was repeated 5 times at the two sites for each animal giving a total of 240 values. It would have been possible to use one site in each animal on 10 occasions. However, this was not done due to fear of possible site trauma by the probe due to multiple placement at the same site damaging the underlying microcirculation. This may influence flux values; it was therefore decided to use two site on 5 occasions in each animal.

Any worry of introducing a spatial related variable to flux values is likely to be unfounced as results from the previous section confirm there is no significant spatial influence on flux.

10.5.4.1 RESULTS

The flux values are tabulated in Table 10.5.3 and 10.5.4 for animals one and two respectively.

	SITE ONE					SITE TWO				
TIME	1	2	3	4	5	6	7	8	9	10
5S	84	114 †	88	119	149 †	102	109	120 †	103	119 †
10S	89	79	89	109	139	104	115	108	112	115
15S	83	85	85	109	145	120	121 †	110	119 †	111
20S	88	86	83 *	109	129	116	113	96 *	113	108
25S	110	91	91	90 *	139	122 †	100 *	109	110	101
30S	104	85	110	122	138	121	121 †	101	107	96 *
35S	90	100	95	131	135	106	105	111	104	107
40S	120 †	107	108	112	131	108	103	112	98	102
45S	84	82	110	125	138	101	111	99	95 *	100
50S	91	71	109	145 †	131	99	121 †	105	111	114
55S	97	68 *	120	136	128 *	91 *	109	113	98	119 †
60S	78 *	81	124 †	140	138	102	111	100	112	104
MEAN	93	87	101	121	137	108	112	107	107	108
%	45	53	41	45	15	29	19	22	23	21

*TABLE 10.5.3 .Variation of flux with time (seconds) in animal 1 measured at 5 second intervals at two sites. † - Maximum Flux * - Minimum Flux*

The mean flux for each 60 second period is calculated. In addition, the difference between the maximum (†) and minimum flux value (*) is expressed as a percentage of the mean. The maximum and minimum flux variation for any given 60 second period for animal one was 53% and 15% of the mean respectively. The corresponding figures for animal 2 were 31% and 8%. For animal 1, the difference between maximum and minimum flux value for the 10 runs was less than 50% of the mean in 9 and less than 25% of the mean on 5 occasions. Similarly, for animal 2, the variation for the 10 runs was less than 30% of the mean in 9 and less than 25% of the mean on 6 occasions. Graph 10.5.7 charts the mean flux for each of the 20 runs in both animals. The error bars (mean plus or minus one standard deviation) are in general narrow especially on the later runs. This suggests

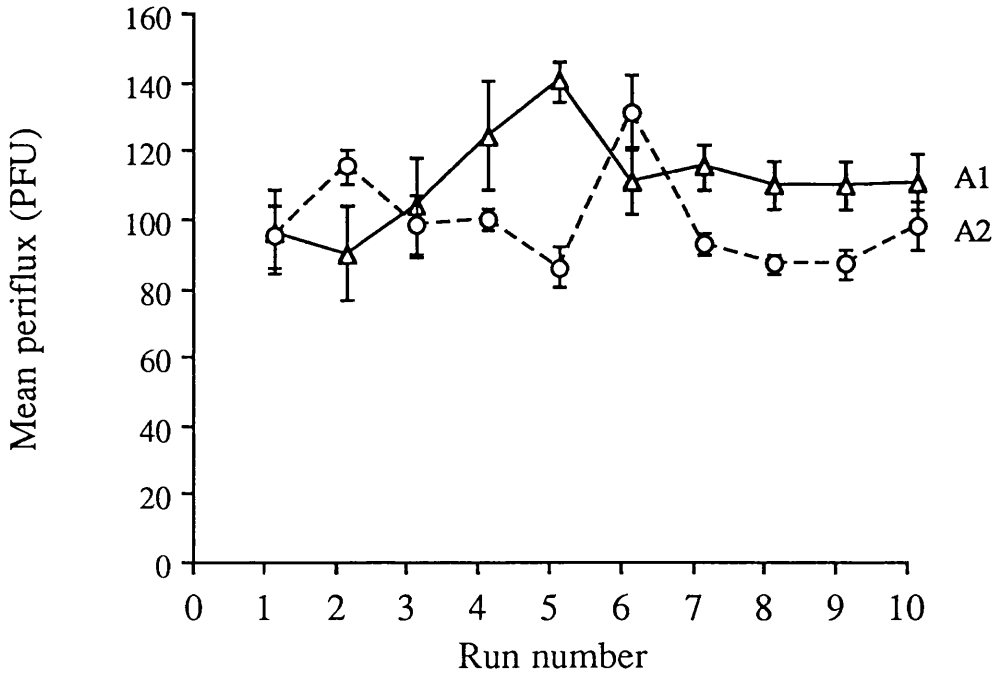
that there is a learning curve to achieving satisfactory probe placement. Once mastered, temporal variation is negligible.

What is the optimum time interval from probe placement to achieving a steady state reading ? One answer is derived by selecting the time window for the total of 20 runs which contains no maximum or minimum flux readings thereby avoiding the extremes of the range. Scrutinising both tables, then for animal one, at 10 and 35 second and for animal two 30 seconds from probe placement produce no flux values at the extremes of the ranges.

	SITE ONE					*SITE TWO*				
TIME	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
5S	*78 **	*116*	*88*	*96*	*74 **	*126*	*86 **	*80 **	*80*	*94*
10S	*81*	*115*	*84*	*94 **	*78*	*109 **	*92*	*81*	*79 * **	*90*
15S	*84*	*123 †*	*103*	*94 **	*79*	*119*	*88*	*83*	*84*	*92*
20S	*86*	*110*	*93*	*96*	*82*	*130*	*92*	*87*	*79*	*117 †*
25S	*90*	*110*	*93*	*98*	*96 †*	*121*	*91*	*82*	*81*	*96*
30S	*91*	*112*	*91*	*98*	*87*	*136*	*89*	*82*	*84*	*91*
35S	*98*	*114*	*92*	*96*	*86*	*149 †*	*88*	*88 †*	*84*	*90*
40S	*103 †*	*110*	*99*	*102 †*	*81*	*138*	*91*	*88 †*	*89*	*93*
45S	*94*	*112*	*83 **	*97*	*79*	*126*	*95 †*	*86*	*87*	*89 **
50S	*99*	*105*	*106*	*100*	*83*	*139*	*93*	*88 †*	*93 †*	*95*
55S	*97*	*104 **	*104*	*95*	*88*	*123*	*88*	*83*	*85*	*98*
60S	*105*	*118*	*108 †*	*100*	*87*	*122*	*92*	*82*	*81*	*95*
MEAN	*92*	*112*	*95*	*97*	*83*	*128*	*90*	*84*	*84*	*95*
%	*23*	*17*	*26*	*8*	*27*	*31*	*10*	*10*	*17*	*29*

*Table 10.5.4. Variation of flux with time in animal 2 measured at 5 second intervals at two sites. † - Maximum flux * - Minumum flux.*

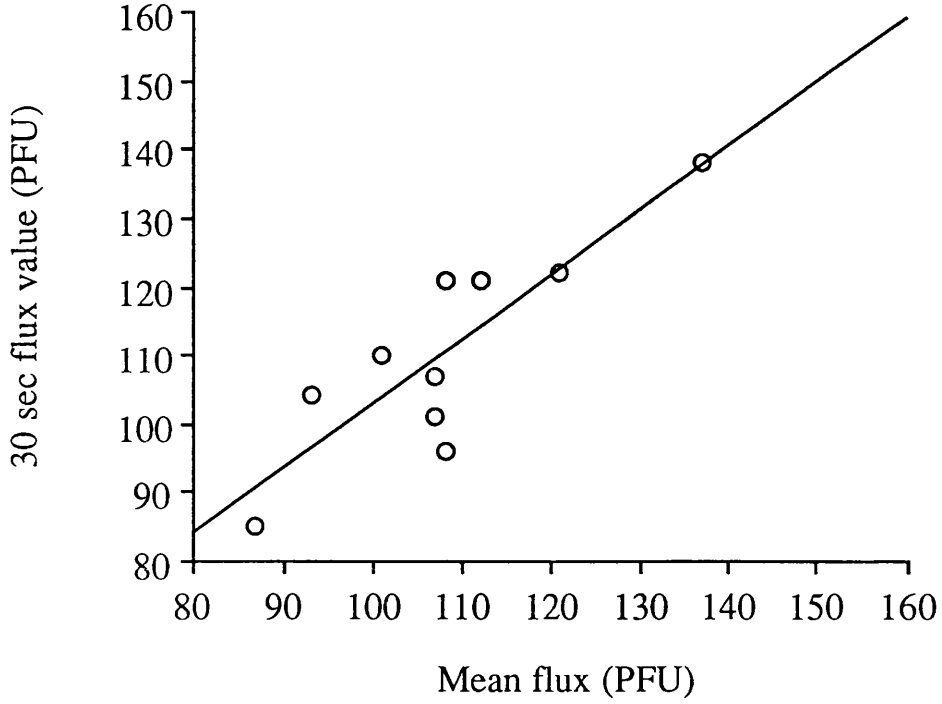
The flux values derived at these times are infact very similar to the average flux for the corresponding run (Table 10.5.5). Graphs 10.5.8 and 10.5.9 illustrate good correlation between flux readings 30 seconds from probe placement and the mean flux of 12 readings over 60 seconds (1 reading every 5 seconds). Thus, flux values taken 30 to 35 seconds from placement are likely to be representative of the true steady flux state.



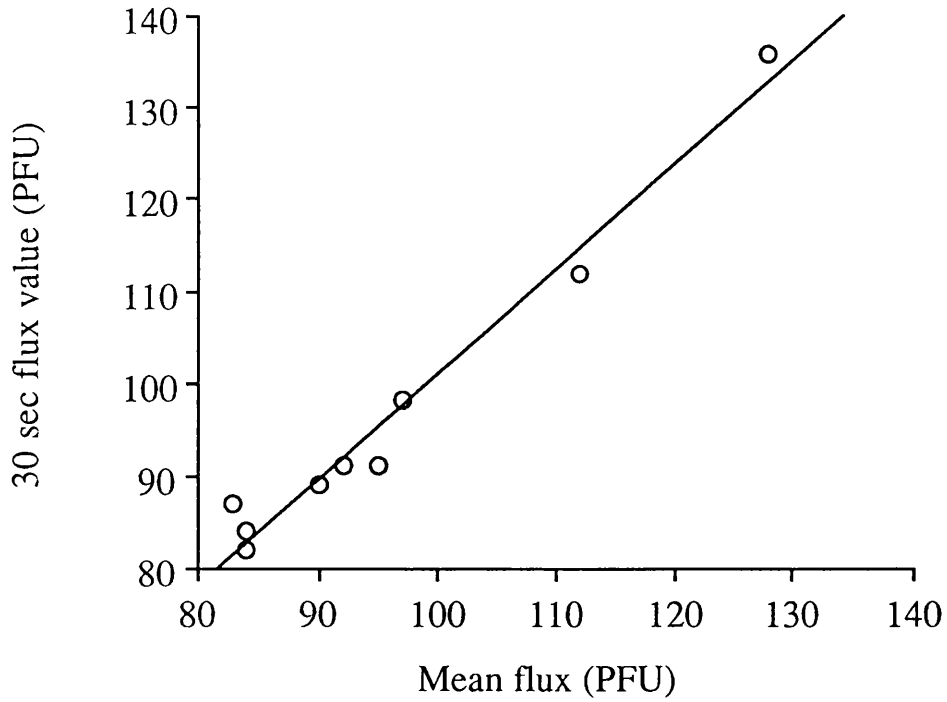
Graph 10.5.7. Comparison of mean flux (± 1 SD) on 10 occasions in animals (A) 1 and 2. Each point is the mean of 12 values taken at 5 second intervals.

RUN	*30S FLUX (A1)*	*MEAN (A1)*	*30S FLUX (A2)*	*MEAN (A2)*
1	*104*	*93*	*91*	*92*
2	*85*	*87*	*112*	*112*
3	*110*	*101*	*91*	*95*
4	*122*	*121*	*98*	*97*
5	*138*	*137*	*87*	*83*
6	*121*	*108*	*136*	*128*
7	*121*	*112*	*89*	*90*
8	*101*	*107*	*82*	*84*
9	*107*	*107*	*84*	*84*
10	*96*	*108*	*91*	*95*

Table 10.5.5. Relationship of flux at 30 seconds from probe placement and mean flux reading in animal 1 (A1) and animal 2 (A2).



Graph 10.5.8. (above) & 10.5.9 (below) - Relationship between mean flux (mean of 12 readings at 5 second increments for 60 seconds from probe placement) and flux value taken 30 seconds from probe placement for animals 1 and 2.



SECTION 2

10.6 LDF ASSESSMENT OF LIVER NECROSIS DURING ILH.

The clinical value of LDF during ILH is as a real time monitoring facility signalling the transition to necrosis of previously viable tissue. The end treatment point will depend upon a relative fall in the flux as flow in the microcirculation progressively decreases and finally ceases. The question addressed in this section is what relative change in the baseline flux translates to irreversible tissue damage at the point of monitoring ?

Initial clinical consideration would suggest placing the sensing probe on the junction of tumour and normal tissue would be most useful. However, there are two important considerations. In clinical practice, satellite nodules invariably reside in the immediate vicinity of hepatic tumour. Secondly, tumour tongues growing from the advancing tumour edge project into the normal liver which cannot be visualised accurately by conventional imaging techniques. Evidence obtained from the surgical literature on hepatic resection suggest that for ILH to achieve effective palliation, a 1 cm rim of normal liver needs to be incorporate into the treatment field (Greenway., 1988). It would therefore seem most logical to commence these experiments in normal animal liver. Successful prediction of necrosis of normal liver beneath the sensing probe should mean all intervening tissue between the laser fibre and the LDF probe will also be necrotic be it all normal liver or a mixture of tumour and normal liver as would the case clinically.

The diameter of the zone of necrosis in rodent liver which might be expected at the energies used in the experiment described below is in the region of 16 mm. If the LDF probe is placed at a point 8 mm away from the laser fibre, it will be at the critical junction between viable and non-viable tissue. Therefore, for rodent liver, this interval would seem ideal for evaluation of LDF.

10.6.1 METHOD

Twenty five adult Wistar rats (180 to 280 gms) were anaesthetised using intramuscular Fentanyl Citrate and Fluanisone (Hypnorm, Janssen Pharmaceuticals Limited, Oxford, UK) at a dose of 0.1 ml per 100 gms body weight. The liver was exposed at laparotomy through a midline incision and the left lobe mobilised and delivered

into the wound to be placed on a moistened gauze swab resting on the anterior abdominal wall. As before, the exposed liver was intermittently irrigated with normal saline at body temperature for the reasons previously mentioned.

The liver was treated using a continuous wave Nd:YAG laser (Model 212, CVI, Albquerque, New Mexico, USA) coupled to a 400 micron fibre optic. The plastic cladding was removed from the distal end of the fibre which was then cleaved. The laser was preset to produce a power of 2.0 watts from the fibre tip which was measured using a power meter (Coherent, UK). Once calibrated, the fibre tip was inserted interstitially into the middle of the left liver lobe to a depth of 2 to 3 mm. A PF302 interstitial probe (Perimed, Sweden) was placed on the liver surface 8 ± 1 mm from the laser fibre (Figure 10.04). The probe was never placed on the peripheral portion of the liver to avoid an edge effect from extension of necrosis. A distance of less than 8 mm between the laser fibre and the LDF probe saturated the PF3 making real time monitoring impossible. Using lower laser power did not influence this critical separation distance.

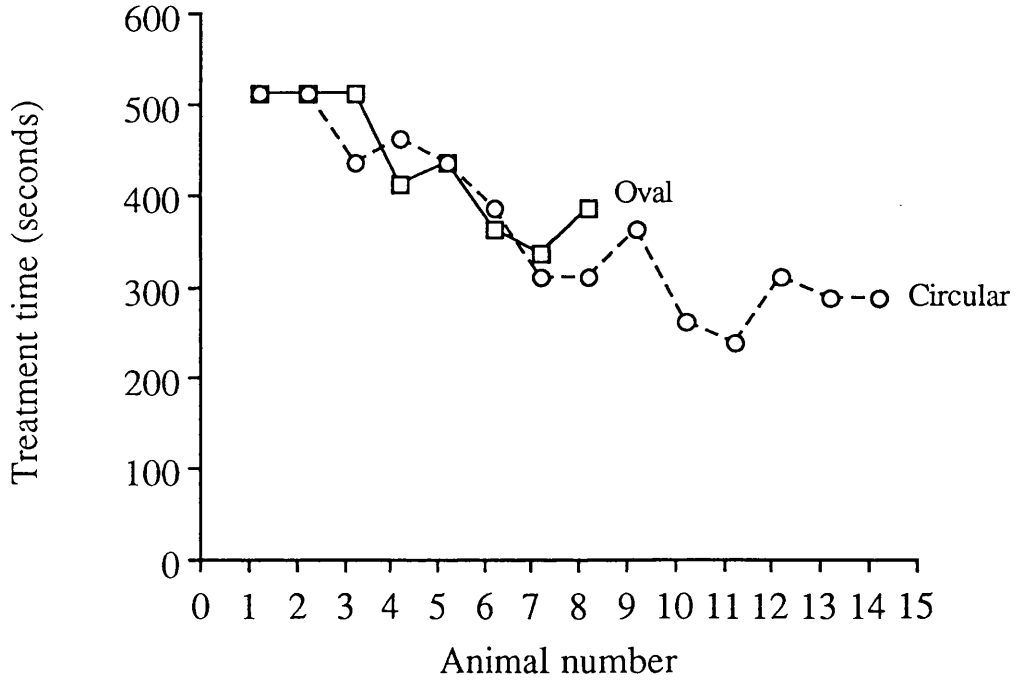
Once a stable baseline flux was established, the liver was photocoagulated at a constant power output of 2.0 watts. A real time flux value was taken every 25 seconds from the onset of coagulation up to a maximum of 500 seconds. Following an initial 2 to 3 fold rise in the flux value, photocoagulation was stopped when the flux reached a level 50% and 25% lower than the baseline reading (group A, n=5 & group B, n=5 respectively), returned to the baseline value (group C, n=7) and fell from an initial peak to a value 50% higher than the baseline reading (group D, n=5). A flux value which on two consecutive readings fulfilled the criteria for each group was accepted as being a representative value. In 3 animals, one of which died later, the flux did not change by any of the criteria stipulated despite a complete treatment of 500 seconds.

Once treatment had stopped, the site of the needle probe was marked carefully with a 5/0 silk suture. The abdominal wall was repaired and the animal allowed to recover to be sacrificed 3 days from treatment. At post mortem, the fibre site was easily identified by its insertion track in the centre of a zone of non-viable liver. The extent of necrosis was measured in 3 dimensions. In particular, the relationship of the extent of necrosis to the

suture noted. Any shortfall or extension of the necrotic area beyond the suture was measured.

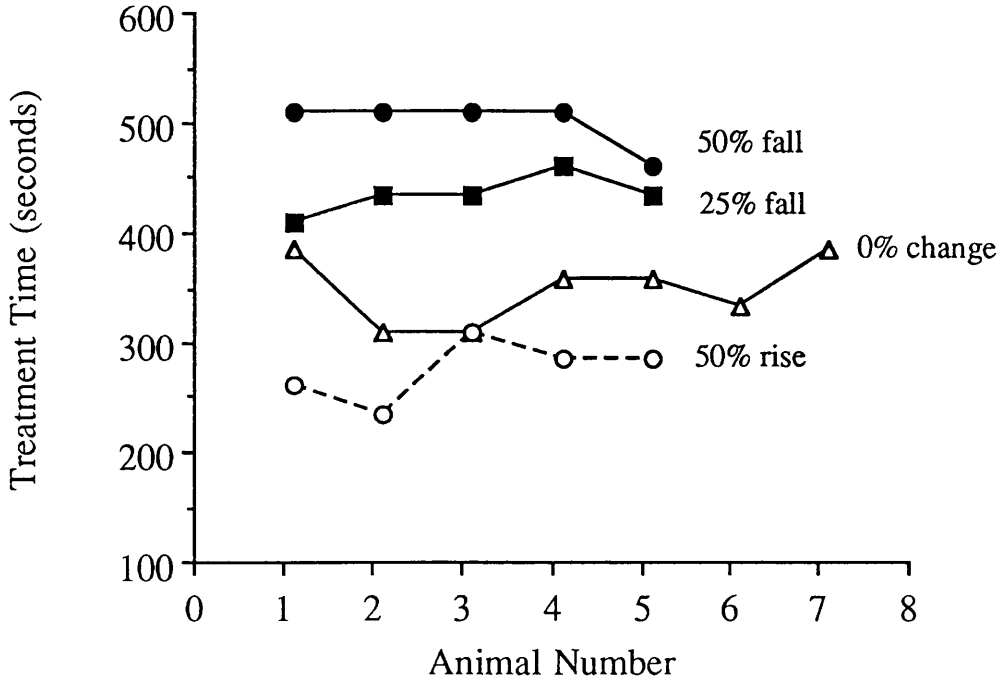
10.6.2 RESULTS

Twenty two animals successfully achieved at least 1 of the 4 criteria for treatment completion, that is a stipulated relative change in baseline flux. The treatment parameters produced in all animals well defined areas of necrosis centred around the fibre tip. In 8 animals, the shape of the necrotic zone was oval and circular in the remaining 14. There was significant overlap in the treatment times producing both patterns (Graph 10.6.1).

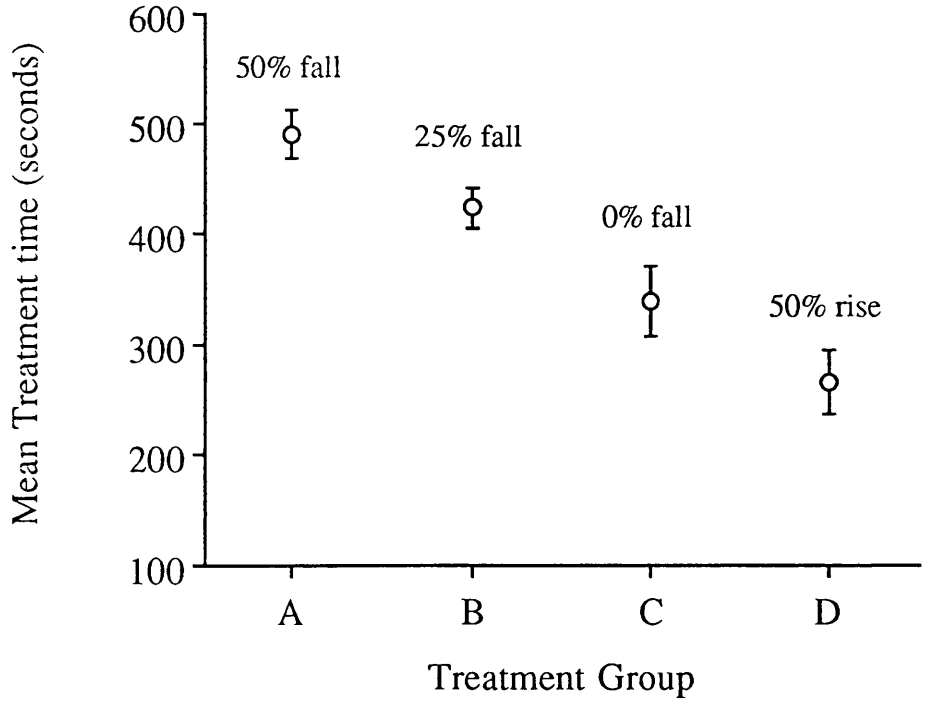


Graph 10.6.1. Relationship between treatment times and shape of necrotic zones.

Appendices X to XIII present flux variation with time for groups A to D respectively. In general, treatment times progressively decreased from group A to D with little overlap between the groups (Graph 10.6.2). The average treatment times were group A 490 seconds, group B 425 seconds, group C 339 seconds and group D 265 seconds. These differences between all groups was statistically significant at the 5% level (Graph 10.6.3).



Graph 10.6.2. Relationship between baseline flux change and treatment times. 0% and 50% change refers to a fall from the peak to baseline and 50% greater than baseline.



Graph 10.6.3. Mean treatment times (± 1 SD) for each treatment group.

The zone of necrosis in groups A and B extended at least to the suture in all animals (Figure 10.05). In no animal was there any viable tissue intervening between the laser fibre and the LDF probe site. In group C and D, 5 out of 7 animals and 1 out of 5 animals respectively had an area of necrosis which extended at least up to the suture. The remaining animals in both these groups exhibited a shortfall of 2 to 3 mm (± 1 mm) from the marking suture. In 3 animals, one of which died soon following treatment, the baseline flux did not change following its initial rise by any of the criteria stipulated. In all, the flux remained elevated by 2 to 3 times the baseline value throughout and immediately at the end of treatment. Of the 2 animals available for autopsy on the third post treatment day, the zone of necrosis extended to but not beyond the site of the LDF probe in both.

10.6.3 DISCUSSION

The oval shape of the necrotic zone arose probably because of an edge effect. Given the relatively small size of vessels in the left lobe of the rat liver, the extension of the necrotic area up to the liver edge is likely to be secondary to thrombosis of a large centrally located vessel and or adjacent collateral vessels. The small peripheral vessels at the liver edge are a significant distance away from the laser fibre and are therefore not occluded by thermal damage. Occlusion of the large central vessel supplying smaller vessels or collaterals by the thermal process deprives the liver edge of its blood supply.

The mean treatment time producing oval zones was 422 seconds compared with 354 seconds for Circular zones. However, there was considerable overlap in treatment times for both groups suggesting a relationship not simply due to treatment energy. A second factor likely to be influential is fibre position relative to critical vessels or collaterals. This phenomena is likely to be irrelevant in human liver due to its size. Lastly, the optical properties of the liver often lead to forward scattering which inturn produces an oval lesion.

The preliminary rise in the flux during the first 50 to 75 seconds from treatment is probably due to a reactive hyperaemic phase as a result of temperature gradients created around the fibre tip. The flux then progressively fell with time. Results from this study suggest a fall of 25% or more in the baseline flux equates with tissue necrosis at the sensing probe and all intervening tissue between it and the laser fibre. Smaller changes in

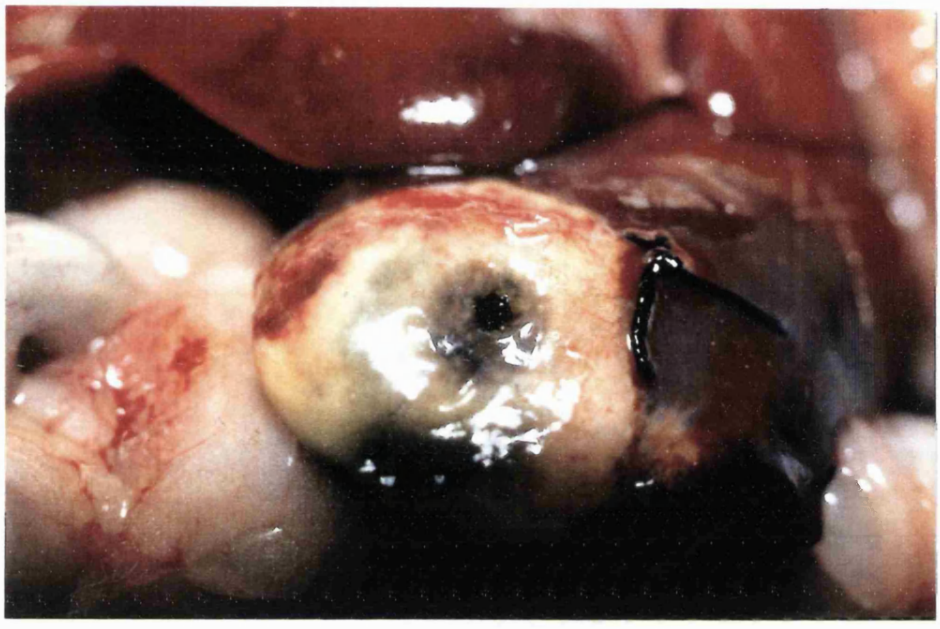


Figure 10.05. Appearance of the left lobe 3 days following treatment. Note the well defined zone of necrosis extending up to the marking silk suture.

flux as seen in groups C and D predicted the extent of necrosis in 70% and 20% of animals respectively. The relative fall in the flux is to some extent a dose dependant phenomenon, with higher treatment energies producing larger falls.

One might postulate that a threshold flux level exists which determines the outcome of laser photocoagulation. A change above or below the threshold determines the balance between viability and non-viability. It therefore seems surprising to see such different threshold values produce comparable necrotic zones in groups A, B and C. It is difficult to explain in pathophysiological terms how a return of the flux to a baseline state following a preliminary rise which is probably hyperaemic in origin (Group C) can equate with necrosis. In addition, 2 out of the 3 animals whose flux readings remained 2 to 3 times the baseline reading at the end of 500 seconds of treatment showed areas of necrosis comparable to those in Group A with non-viable tissue up to the level of the LDF probe.

It is difficult to make sense of these results. It would appear that large relative falls (up to 50%), no change and two to three fold increases in baseline flux all translate to tissue necrosis. However, some encouragement can be drawn from two sources. No animal showing relative falls in baseline flux of 25% or 50% had viable liver at the monitoring site. Secondly, there is a rough quantitative relationship between treatment times and the extent of relative falls in the baseline flux.

A possible reason for the confusing results may be due to the Nd:YAG laser influencing the PF3. It has been noted that close proximity of the sensing probe ($\leq 6 \pm 1$ mm) to the laser fibre causes photodetector saturation which then registers overload. Laser noise with interfering frequencies from the Nd:YAG laser swamp the photodetector which is unable to pick up the more subtle flux correlated signal from the He-Neon laser. Slightly longer separations (8 ± 1 mm), reduced the influence of the ND:YAG laser but may still have been sufficient to interfere with flux readings. Therefore, it could be that relative falls in baseline flux of 50%, 25%, and 0% infact represent a 75%, 50% and 25% fall. The situation has been discussed with the manufacturers (Perimed, Sweden) who accept the potential for the Nd:YAG laser to interfere with flux readings. In principle, it was felt that the problem could be easily overcome by fitting a filter which suppresses extraneous laser noise from the Nd:YAG wavelength. This experiment would need to be repeated with a

suitable modified PF3 meter to see if a clearer relationship between flux and tissue viability can be found. If despite suitable modification of the PF3 no clear relationship can be found, then it may be worth considering alternative interstitial monitoring techniques. Temperature monitoring using micro-thermocouples, changes in laser light transmission through the tissues as its optical properties alter or lastly, measuring changes in oxygen tension are worthy of consideration.

However, if a clear relationship between flux changes and tissue necrosis can be established, then a potential role for LDF monitoring in clinical practice exists. The interstitial probe is of a sufficiently narrow calibre allowing percutaneous placement under US or CT control. Despite a movement artefact filter, large respiratory excursions can produce unstable readings. As has been mentioned before, LDF provides a point assessment, that is only the fate of tissue at the reference probe can be evaluated. By implication, the viability of tissue in a straight line between the laser fibre and the needle probe can be judged. Unfortunately, in clinical practice, tumours are rarely perfectly round well defined structures. Thus, the fate of tissues in juxtaposition to the sensing probe cannot be reliably assessed. However, these limitations can be overcome by combining LDF assessment with a more general imaging modality such as US or CT. The future role of pathophysiological monitoring as provided by LDF is surely going to be complementary and not an alternative to conventional imaging techniques.

CHAPTER 11. FUTURE OF ILH

Despite advances in oncology, the palliative management of solid organ cancers is unsatisfactory. ILH is a novel approach to the problem, although the technique remains in its infancy. Preliminary results of feasibility studies presented in this thesis (chapters 6,7 and 8) suggest there are exciting potentials for the future treatment of liver, pancreatic and breast cancer. For the moment, ILH remains a palliative modality but with further advances and refinements, the prospect for cure exists.

Understanding laser tissue interaction and monitoring the ensuing biological effect remain fundamental to the safe and effective application of ILH. The work in chapter 9 goes some way to evaluating the practical implications of tissue optical characteristics (normal versus tumour) on the nature and extent of the biological effect. Finally a novel approach to monitoring the biological effect using LDF as evaluated in chapter 10 suggests that this technique may have a useful complimentary role to conventional imaging.

What of the future of ILH ? I believe the prospects are good but much work, both experimental and clinical needs to be carried out before ILH can be regarded as an established technique challenging the role of more conventional treatments. This chapter highlights by organ future areas of potential research and development.

11.1 LIVER

The most important principle of ILH in oncology is matching the extent of laser mediated necrosis to the tumour volume under consideration. More precise tumour mapping using CT or MR will not only improve tumour delineation but enhance precision of needle placement and separation especially when treating small relatively inaccessible metastases. To date, there is relatively little information comparing the radiological tumour extent with true tumour dimensions in resected liver or at post mortem. A comparative study of US, CT and MRI to assess the most accurate technique for tumour delineation and fibre position would useful. An allowance for any inherent shortfall or excess in tumour extent peculiar to a given imaging modality can then be made with precision thus minimising the risk of incomplete tumour treatment.

To-date, US has been the cornerstone of real time imaging. Exciting developments in imaging and laser technology mean that CT and MRI will challenge the role of US. Fourth generation CT scanners capable of very rapid sequential scanning could in theory provide real time images during laser therapy. Wider availability of MRI with developments in suitable contrast media such as supraparamagnetic iron could make this technique superior to CT for tumour delineation and real time imaging. Recent developments in semi-conductor laser technology mean that suitable multiport lasers are smaller and sufficiently portable to be transported in a medium size suitcase. These lasers are capable of running off a domestic power point without need for cumbersome external cooling circuits and can therefore be used in conventional CT or NMR suites without expensive modifications.

These alternative monitoring techniques should allow residual viable tumour to be immediately identified and treated. The gain would be increased confidence in complete tumour treatment at a given session. With a reduction in the total number of treatments necessary to achieve complete tumour eradication, any risk to the patient will be reduced. However, before this becomes a realistic proposition, a study correlating the extent of real time and final changes from US, CT and MR images with the true pathological extent of tumour necrosis is required. The simplest way to achieve this would involve offering laser treatment prior to surgery in patients with hepatic metastases destined for resection. Such a study may be fraught with tough ethical considerations in so much that patients with potentially curative disease are subjected to an unnecessary treatment which may reduce the chances of cure. However, this approach would identify the most reliable real time imaging technique which could then be employed with real confidence in the knowledge that what is seen radiologically actually reflects the true extent of tumour necrosis.

As a corollary, the influence of time from treatment to post treatment imaging (CT and MRI) in assessing changes in the extent of tumour necrosis and healing with histological correlation is important. Clearly, undue delay in surgical resection would be unacceptable and therefore relatively long follow up histological data is unlikely to be forthcoming. however, that data accrued could allow treatment and follow up imaging protocols to be drawn up for visualising the maximal extent of necrosis, residual or recurrent tumour and complete healing of treated metastases. This would reduce

unnecessary laser treatments, inappropriate follow up imaging and identify metastases at risk of early relapse.

The surgical literature has clearly shown high local recurrence rates if hepatic resection is undertaken with a tumour free margin of less than 10 mm (Greenway., 1988). This has important implications for ILH. Achieving optimum local control will require incorporation at least a 1 cm margin of 'normal' liver around a metastasis into the treatment zone. A study evaluating the influence of incorporating a margin (1, 2 or 3 cm) of 'radiologically normal' liver on local tumour growth would identify the most appropriate radiological safety margin for inclusion into the treatment field. This may have important implications when considering treatment of metastases close to vital structures, for example, the inferior vena cava.

An alternative approach to enhancing tumour eradication may be possible by combining ILH with photodynamic therapy. This technique relies on preferential tumour uptake of a harmless photosensitiser which is activated by a specific wavelength of laser light into a cytotoxic intermediate, most effective at dealing with microscopic tumour deposits. ILH could therefore be used to debulk the main tumour mass with PDT mopping up any viable residual tumour cells. Given that hyperthermia enhances the efficacy of chemotherapy without potentiating the side effects, then combining ILH with regional chemotherapy is an attractive treatment concept. A trial comparing the influence of combined chemotherapy plus ILH on tumour control would be instructive. If chemotherapy provided a useful adjuvant role, then the optimum agent or combination of agents, route and time of administration in relation to laser therapy may yield further benefits.

The role of interstitial monitoring modalities in enhancing real time assessment of the extent of tumour necrosis is important. A detailed real time picture would allow appropriate adjustments in laser parameters or fibre position to be made during or immediately following photocoagulation thus reducing the risk of incomplete treatment. Available techniques include temperature measurement, changes in laser light transmission, tissue oxygen tension and changes in blood flow. For the moment, all remain incompletely evaluated. Ultimately, a comparative trial of all four techniques would yield the most effective to be used with either CT or MRI.

Investigating alternative laser wavelengths which maybe more appropriate to the optical characteristics of tumour may optimise dosimetry. There is no theoretical limitation to the number of fibres that can be used to treat a given tumour. However, the fate of large areas of laser induced necrosis in the liver should be studied before using large numbers of fibres in a clinical setting. The advantages are obvious. Increased confidence in treating large tumours completely with no fibre manipulation and shorter treatment time.

Work from chapter 6 has shown that ILH is most effective for smaller metastases. Identifying metastases at the earliest possible stage may enhance the chances of successful eradication and possible cure. Adopting an aggressive follow up protocol especially in relatively young patients may yield metastases at a size when effective palliation or even cure may be more easily achieved. What of patients with potential synchronous metastases undetected by palpation at laparotomy ? Intra-operative ultrasound allows reliable detection of metastases down to 0.4 cm in diameter. A selective policy of intra-operative sonographic screening of the liver could yield a harvest of patients with tiny metastases which may be treated at the time of primary tumour resection. ILH may also have a complimentary role to hepatic resection. For example, the patient with resectable disease in one lobe yet has one or two small metastases in the opposite lobe which are unresectable or whose removal would fail to leave sufficient functional hepatic parenchyma. A combined approach with resection of the predominantly involved lobe and laser therapy to lesions in the adjacent lobe may achieve the therapeutic objective at lower risk. Ultimately, the influence of ILH on quality of life and survival requires evaluating which if favourable may lead to a controlled trial of hepatic resection versus ILH for discrete hepatic metastases. Alternative interstitial techniques such as cryotherapy and alcohol therapy will need to be considered and evaluated against ILH in the context of a controlled trial.

11.2 PANCREAS

Much of what has been said in section 11.1 is applicable to pancreatic cancer. The anatomical position of the organ and aggressive disease biology form formidable obstacles to the success of laser therapy. Invasive techniques such as intra-operative radiotherapy have successfully achieved local tumour control but this has not translated to increased

survival although the palliative benefit is more difficult to assess. The goal for ILH is to achieve comparable local control rates (> 90%) as intra-operative radiotherapy without the morbidity and mortality that is commensurate with a laparotomy. Even if ILH could be refined to such an extent, therapeutic failure is likely due to the high incidence of nodal and blood borne spread. Any measurable improvement in survival will only occur if suitable adjuvant therapy can be combined with ILH. Possible candidates include chemotherapy and photodynamic therapy. The latter could be directed against nodal and peri-pancreatic deposits while ILH deals with the main tumour. This area is currently the focus of active research.

11.3 BREAST

Most surgeons agree that surgery to the axilla is an integral part of treatment of operable invasive breast cancer. If ILH is used to treat invasive breast cancer, then it makes no considerations for dealing with the axilla. Employing ILH to treat the breast lesion and surgery to tackle the axilla is not logical or practical. However, a small subset of patients with invasive breast cancer such as those with medial tumours and post menopausal patients who are invariably placed on Tamoxifen regardless of nodal status may be suited to laser treatment. However, before ILH can be used as a primary treatment for loco-regional control, several problems need to be addressed.

As for the liver and pancreas, a study correlating the histological tumour extent in resected specimens with radiological dimensions from mammograms, US, CT and MRI is required. This is particularly important in the breast given the high incidence of tumour foci adjacent to the main tumour. As discussed for hepatic metastases, tumour free margin around the tumour (at least 2 cm) needs to be incorporated into the treatment area if acceptable local recurrence rates are to be achieved despite adjuvant therapy such as radiotherapy and Tamoxifen. The extent of this margin is likely to be 1 to 2 cm but work to confirm this by correlating local recurrence rates with the extent of apparently tumour free tissue treated is desirable.

Establishing reliable radiological end treatment points from CT, MR, US or mammographic images with histological correlation is important to be confident of

successful tumour eradication. In addition, radiological delineation of tumour regression, progression, healing and possible recurrence is important in identifying therapeutic failures and potential patients for salvage surgery. This can be done by matching histological appearances with post treatment radiology following tumour resection at various intervals from laser treatment. This will also help define optimum laser parameters which can be related to tumour volume and extent of necrosis.

In-situ lobular and ductal breast carcinoma have a very high incidence of multifocality. Theoretically the absence of nodal disease makes this group an attractive treatment proposition for ILH. The problems of reliable histological diagnosis of in-situ carcinoma without the benefit of a surgical specimen needs to be resolved before ILH therapy for *in-situ* tumour can be contemplated. However, the obstacle of untreated multifocal disease needs to be addressed. Tamoxifen or radiotherapy may be one answer but more exciting is the concept of PDT which is particularly suited to treating organs such as the bladder or breast where the epithelium of the whole organ is potentially unstable. Basic work on dosimetry, sensitizer doses, preferential tumour to normal ratios, interval from administration to treatment, the influence of PDT on normal breast tissue and mechanisms of healing is required.

In conclusion, the work in this thesis has shown that ILH is a feasible technique for inducing necrosis safely in tumours of the liver, pancreas and breast. The challenge for the future is to refine this technique to make it a useful and practical clinical therapy. Much experimental and clinical work is required by non-clinical and clinical workers before ILH can assume the mantle of alternative established techniques in oncological practice.

APPENDIX I. Relationship of mean necrosis diameter & volume to mean tumour diameter & volume.

Patient	*Tumour diameter (cm)*	*Tumour volume (cm^3)*	*Necrosis diameter (cm)*	*Necrosis volume (cm^3)*	*Percentage necrosis*	*Necrosis grade*
M.B	*4.0*	*34.0*	*2.0*	*4.0*	*13*	*III*
J.B	*5.0*	*66.0*	*3.5*	*23.0*	*35*	*III*
R.C	*1.5*	*2.0*	*1.3*	*1.2*	*67*	*II*
	5.0	*5.0*	*4.5*	*48.0*	*73*	*II*
	1.5	*2.0*	*1.2*	*1.0*	*50*	*II*
M.C	*1.5*	*2.0*	*1.5*	*1.8*	*100*	*I*
	3.0	*14*	*2.6*	*9.2*	*67*	*II*
	2.5	*8.0*	*2.2*	*5.6*	*68*	*II*
F.H	*8.0*	*269.0*	*3.5*	*21.5*	*8*	*III*
G.P	*6.0*	*113.0*	*4.0*	*34.0*	*30*	*III*
	4.0	*34.0*	*3.0*	*14*	*42*	*II*
	4.0	*34.0*	*2.5*	*8.2*	*24*	*II*
	4.0	*34.0*	*2.3*	*6.4*	*19*	*II*
	2.0 x 4	*4.0 x 4*	*2.0 x 4*	*4.2 x 4*	*100 x 4*	*I x 4*
B.R	*5.0*	*66.0*	*2.5*	*8.2*	*12*	*III*
J.S	*2.0*	*4.0*	*2.0*	*4.0*	*100*	*I*
	2.5	*8.0*	*2.3*	*6.4*	*78*	*II*
	5.0	*66.0*	*3.8*	*2.9*	*44*	*III*
	4.0	*34.0*	*2.5*	*8.2*	*24*	*III*
W.T	*6.0*	*113.0*	*2.0*	*4.2*	*5*	*III*
A.T	*11.0*	*699.0*	*2.5*	*8.2*	*1.0*	*III*
D.W	*4.0*	*34.0*	*3.0*	*14*	*41*	*III*
	2.0	*4.0*	*1.3*	*1.2*	*29*	*III*
	1.5	*2.0*	*1.5*	*1.8*	*100*	*I*
H.Y	*5.0*	*66.0*	*3.9*	*31*	*47*	*III*
	3.0	*14.0*	*2.5*	*8.2*	*60*	*II*
	3.0	*14.0*	*3.0*	*14*	*100*	*I*
	2.0	*4.0*	*1.8*	*3.0*	*72*	*II*
	2.0	*4.0*	*1.6*	*2.2*	*52*	*II*
	1.0	*0.5*	*0.8*	*0.3*	*51*	*II*

APPENDIX II. Patient details and summary of results.

patient	*age & gendre*	*primary tumour site*	*no. of hepatic tumours*	*tumour diam. (cm)*	*no. of laser R*	*necrosis grade*	*survival from R*	*current status*
M.B	*67 M*	*Rectal*	*1*	*4.0*	*4*	*III*	*40/12*	*Dead*
J.B	*70 M*	*Rectal*	*1*	*5.0*	*1*	*III*	*6/12*	*Dead*
R.C	*67 M*	*Rectal*	*3*	*1.5* *5.0* *1.5*	*5*	*II* *II* *II*	*14/12*	*Alive*
M.C	*62 F*	*Colon*	*3*	*1.5* *5.0* *1.5*	*4*	*I* *II* *II*	*29/12*	*Alive*
F.H	*77 F*	*Colon*	*1*	*8.0*	*4*	*III*	*30/12*	*Dead*
G.P	*53 M*	*Colon*	*8*	*6.0* *4.0 x 3* *2.0 x 4*	*8*	*III* *II x 3* *I x 4*	*16/12*	*Dead*
B.R	*68 M*	*Colon*	*1*	*5.0*	*1*	*III*	*4/12*	*Dead*
J.S	*54 F*	*Colon*	*4*	*2.0* *2.5* *5.0* *4.0*	*4*	*I* *II* *III* *III*	*27/12*	*Dead*
W.T	*58 M*	*Gastric*	*1*	*6.0*	*4*	*III*	*8/12*	*Dead*
A.T	*56 M*	*Oesph.*	*1*	*11.0*	*4*	*III*	*6/12*	*Dead*
D.W	*69 F*	*Colon*	*3*	*4* *2* *1.5*	*5*	*II* *II* *I*	*29/12*	*Alive*
H.Y	*68 F*	*Small bowel carcin-oid*	*6*	*5.0* *3.0* *3.0* *2.0 x 2* *1.0*	*8*	*III* *II* *I* *II x 2* *II*	*26/12*	*Alive*

APPENDIX III. Absolute and mean tumour diameters.

PATIENT	*TUMOUR DIMENSIONS (cm)*	*MEAN TUMOUR DIAMETER (cm)*
M.B	*3.0 x 4.0 x 3 .5*	*4.0*
J.B	*5.0 x 5.5 x 4.5*	*5.0*
R.C	*4.5 x 5.5 x 4.5*	*5.0*
	1.5 x 1.5 x 1.6	*1.5*
	1.5 x 1.5 x 1.3	*1.5*
M.C	*2.5 x 3.3 x 2.5*	*3.0*
	1.5 x 1.3 x 1.6	*1.5*
	2.2 x 2.3 x 2.6	*2.5*
F.H	*7.5 x 8.2 x 7.7*	*8.0*
G.P	*6.5 x 5.5 x 5.7*	*6.0*
	4.5 x 3.5 x 4.0	*4.0*
	4.2 x 3.5 x 3.3	*4.0*
	5.0 x 4.0 x 3.5	*4.0*
	2.0 x 2.2 x 2.0	*2.0*
	2.0 x 1.5 x 1.5	*2.0*
	2.5 x 1.5 x 1.0	*2.0*
	1.5 x 2.2 x 2.4	*2.0*
B.R	*5.0 x 4.6 x 4.7*	*5.0*
J.S	*2.0 x 2.0 x 1.6*	*2.0*
	3.0 x 2.5 x 1.7	*2.5*
	3.0 x 4.0 x 4.8	*4.0*
	4.5 x 4.0 x 6.4	*5.0*
W.T	*6.3 x 5.6 x 5.3*	*6.0*
A.T	*15.0 x 12.0 x 5.3*	*11.0*
D.W	*4.5 x 3.7 x 2.9*	*4.0*
	1.5 x 1.5 x 1.3	*1.5*
	2.0 x 1.9 x 2.2	*2.0*

H.Y	*5.0 x 5.1 x 4.8*	*5.0*
	3.3 x 2.7 x 2.5	*3.0*
	3.0 x 2.5 x 2.5	*3.0*
	2.4 x 2.0 x 1.7	*2.0*
	2.0 x 1.2 x 2.4	*2.0*
	1.0 x 1.0 x 0.8	*1.0*

APPENDIX IV. Patients receiving chemotherapy.

Patient	*Before ILH*	*During ILH*	*After ILH*
M.B	*No*	*No*	*Yes*
J.B	*No*	*No*	*No*
R.C	*Yes*	*Yes*	*No*
M.C	*Yes*	*Yes*	*Yes*
F.H	*No*	*No*	*No*
G.P	*Yes*	*Yes*	*Yes*
B.R	*No*	*No*	*No*
J.S	*No*	*No*	*Yes*
W.T	*Yes*	*No*	*No*
A.T	*No*	*No*	*No*
D.W	*No*	*No*	*No*
H.Y	*No*	*No*	*No*

APPENDIX V. CEA titres & treatment dates.

Patient	*Date of CEA*	*CEA titre (0-9 IU/L)*	*Treatment date*
M.B	*July 1988*	*14*	*July 1988*
	September 1988	*44*	*September 1988*
	July 1989	*230*	*January 1989*
	November 1989	*550*	*October 1989*
R.C	*June 1991*	*17*	*July 1991*
	July 1991	*16*	*August 1991*
	August 1991	*39*	*November 1991*
	November 1991	*32*	*March 1992*
			April 1992
M.C	*March 1990*	*4*	*April 1990*
	November 1990	*11*	*June 1990*
	December 1990	*15*	*February 1991*
	January 1991	*21*	*June 1991*
	April 1991	*31*	
	June 1991	*54*	
	July 1991	*72*	
F.H	*October 1989*	*69*	*January 1990*
	February 1990	*213*	*March 1990*
	June 1990	*407*	*March 1990*
			May 1990
J.S	*April 1989*	*6*	*June 1989*
	October 1989	*13*	*November 1989*
	July 1990	*312*	*March 1990*
	August 1990	*400*	*March 1990*
D.W	*November 1989*	*12*	*February 1990*
	July 1990	*27*	*March 1990*
	September 1990	*32*	*July 1990*
	November 1990	*74*	*October 1990*
			October 1990

APPENDIX VI. Transplanted tumours: spontaneous necrosis in 10, 15, 20, & 30 mm diameter tumour cohorts (10 animals per cohort).

Tumour diam. (mm)	Growth time (days)	Length (mm)	Width (mm)	Hight (mm)	Necrosis diam. (mm)
10	8	9	8	8	0
	10	10	9	8	0
	12	9	10	8	0
	12	11	10	10	2
	10	10	9	9	0
	8	9	9	9	0
	10	10	10	8	0
	14	11	10	9	0
	12	11	11	10	2
	11	10	11	10	2
15	16	14	13	10	4
	16	15	13	11	7
	18	15	15	11	6
	20	16	14	10	5
	16	15	13	11	6
	16	14	14	10	6
	18	15	15	11	5
	20	16	15	10	6
	18	16	14	11	6
	16	15	14	11	5
20	20	20	19	15	15
	20	21	18	15	12
	18	20	18	14	10
	18	19	17	15	9
	20	20	20	16	11
	18	20	21	15	7
	18	19	20	14	8
	22	21	20	16	8
	22	20	18	15	10
	20	21	21	16	10
30	25	25	24	20	8
	27	24	19	15	10
	23	27	20	18	11
	25	26	21	18	12
	29	25	19	19	12
	25	25	20	20	10
	27	25	22	17	10
	29	24	18	16	11
	30	26	23	20	15
	31	25	20	19	12

APPENDIX VII. Change in tumour volume in control cohort at 5 days starting from a diameter of 10 mm.

Cohort	Tumour size (mm)	Tumour vol. (mm^3)	Tumour size at 5 days (mm)	Tumour vol. at 5 days (mm^3)	Tumour vol. change (mm^3)
Control	10 x 10 x 11	0.6	16 x 14 x 11	1.9	1.3
	9 x 8 x 8	0.3	15 x 14 x 10	1.8	1.5
	10 x 10 x 10	0.5	14 x 14 x 12	1.8	1.3
	11 x 11 x 10	0.6	15 x 15 x 10	1.8	1.2
	10 x 8 x 8	0.3	15 x 13 x 11	1.8	1.5
	10 x 9 x 9	0.4	15 x 14 x 10	1.8	1.4
	10 x 9 x 7	0.3	14 x 13 x 9	1.3	1.0
	11 x 9 x 8	0.4	14 x 14 x 11	1.6	1.2

APPENDIX VIII. Laser mediated necrosis: change in tumour volume at 5 days for each treatment cohort (7 animals per cohort).

Treatment cohort	Tumour size at 5 days (mm)	Tumour vol. (mm^3)	Ulcer size at 5 days (mm)	Ulcer 'vol.' at 5 days (mm^3)	Tumour vol. change (mm^3)
2.0w.200s	16 x 16 x 10	2.0	10 x 10 x 5	0.4	1.1
	18 x 14 x 7	1.4	10 x 10 x 4	0.3	0.6
	18 x 18 x 5	1.3	9 x 9 x 5	0.3	0.5
	17 x 17 x 8	1.8	7 x 7 x 5	0.2	1.1
	15 x 15 x 8	1.4	9 x 7 x 4	0.2	0.7
	17 x 15 x 5	1.0	8 x 8 x 3	0.15	0.4
	16 x 16 x 5	1.0	8 x 7 x 3	0.13	0.4
2.0 W.300s	16 x 16 x 10	2.0	13 x 11 x 6	0.7	0.8
	20 x 18 x 7	2.3	12 x 12 x 6	0.7	1.1
	18 x 18 x 6	1.5	14 x 10 x 6	0.7	0.3
	20 x 20 x 8	2.5	14 x 14 x 5	0.8	1.2
	20 x 18 x 5	1.3	12 x 10 x 6	0.6	0.2
	20 x 20 x 6	1.9	10 x 10 x 6	0.5	0.9
	0 x 0 x 0	0	All ulcer	0	- 0.5
2.0 W. 400s	20 x 18 x 7	1.7	12 x 12 x 6	0.7	0.5
	20 x 20 x 8	2.5	14 x 14 x 7	1.0	1.0
	16 x 16 x 10	2.0	15 x 13 x 8	1.2	1.2
	0 x 0 x 0	0	All ulcer	0	- 0.5
	0 x 0 x 0	0	All ulcer	0	- 0.5
	0 x 0 x 0	0	All ulcer	0	- 0.5
	0 x 0 x 0	0	All ulcer	0	- 0.5
2.0 W. 500s	16 x 16 x 7	1.4	6 x 6 x 8	0.2	0.7
	15 x 13 x 8	1.2	8 x 8 x 8	0.4	0.3
	0 x 0 x 0	0	All ulcer	0	- 0.5
	0 x 0 x 0	0	All ulcer	0	- 0.5
	0 x 0 x 0	0	All ulcer	0	- 0.5
	0 x 0 x 0	0	All ulcer	0	- 0.5
	0 x 0 x 0	0	All ulcer	0	- 0.5
2.0 W. 700s	19 x 17 x 10	2.5	16 x 15 x 8	1.6	0.4
	24 x 20 x 10	3.8	18 x 18 x 10	2.5	0.8
	0 x 0 x 0	0	All ulcer	0	- 0.5
	0 x 0 x 0	0	All ulcer	0	- 0.5
	0 x 0 x 0	0	All ulcer	0	- 0.5
	0 x 0 x 0	0	All ulcer	0	- 0.5
	0 x 0 x 0	0	All ulcer	0	- 0.5

2.0 W.	20 x 20 x 9	2.8	18 x 18 x 10	2.5	- 0.2
	18 x 18 x 10	2.5	16 x 16 x 10	2.0	0
1000s	20 x 16 x 9	2.3	16 x 16 x 8	1.6	0.2
	0 x 0 x 0	0	All ulcer	0	- 0.5
	0 x 0 x 0	0	All ulcer	0	- 0.5
	0 x 0 x 0	0	All ulcer	0	- 0.5
	0 x 0 x 0	0	All ulcer	0	- 0.5

APPENDIX IX. Survival (days) from a diameter of 10 mm in control cohort (n=8 animals) & from laser therapy in treatment cohort (n= 7 animals).

Control	2.0 W for 200 secs	2.0 W for 300 secs	2.0 W for 400 secs	2.0 W for 500 secs	2.0 W for 700 secs	2.0 W for 1000 secs
13	22	41	49	71	90	90
20	31	37	37	61	90	90
17	28	41	40	90	35	90
13	25	40	90	64	39	37
13	31	42	90	90	40	42
15	27	35	90	90	56	60
17	25	32	45	40	70	65
15						

APPENDIX X. Time (seconds) to achieve a 50% fall in baseline periflux (PFU) value in 5 animals at a laser power of 2.0 watts.

Time (secs)	Animal 1 (PFU)	Animal 2 (PFU)	Animal 3 (PFU)	Animal 4 (PFU)	Animal 5 (PFU)
Base PFU	120	130	80	100	110
Target PFU	60	75	40	50	55
25	202	271	96	232	239
50	196	300	78	266	230
75	200	275	82	227	198
100	180	199	67	206	200
125	215	157	58	210	185
150	198	189	62	200	172
175	169	177	58	186	175
200	150	154	63	169	160
225	135	156	60	149	147
250	106	153	58	114	139
275	108	100	55	109	143
300	97	111	49	111	126
325	85	95	52	99	119
350	75	88	50	88	93
375	77	81	54	76	80
400	72	86	47	73	64
425	64	83	45	62	52
450	69	90	43	56	47
475	59	76	40	48	
500	55	74	38	51	

APPENDIX XI. Time (seconds) to achieve a 25% fall in baseline periflux (PFU) value in 5 animals at a laser power of 2.0 watts.

Time (secs)	Animal 1 (PFU)	Animal 2 (PFU)	Animal 3 (PFU)	Animal 4 (PFU)	Animal 5 (PFU)
Base PFU	85	100	110	90	82
Target PFU	64	75	82	67	61
25	250	239	235	216	250
50	288	219	185	200	277
75	212	200	196	224	220
100	191	180	153	181	189
125	172	192	145	181	200
150	156	176	119	196	184
175	150	180	134	156	199
200	120	160	112	133	180
225	112	146	110	127	167
250	95	125	89	118	149
275	98	112	92	120	132
300	92	105	122	95	110
325	71	111	99	95	96
350	72	94	105	87	84
375	65	83	95	88	77
400	62	72	82	72	62
425		66	75	65	61
450				63	
475					
500					

APPENDIX XII. Time (seconds) to achieve a return to baseline periflux (PFU) value in 7 animals at a laser power of 2.0 watts.

Time (secs)	Animal 1 (PFU)	Animal 2 (PFU)	Animal 3 (PFU)	Animal 4 (PFU)	Animal 5 (PFU)	Animal 6 (PFU)	Animal 7 (PFU)
Base (PFU)	85	110	105	100	90	100	80
Target (PFU)	85	110	105	100	90	100	80
25	199	210	153	200	264	242	195
50	238	200	150	227	210	208	212
75	243	177	129	194	167	188	219
100	236	187	132	184	151	126	200
125	186	175	130	232	126	120	176
150	172	159	127	178	112	106	183
175	138	140	119	172	114	118	155
200	115	128	116	151	106	120	136
225	98	120	112	131	100	127	102
250	100	113	109	112	97	119	92
275	107	109	103	120	92	110	78
300	101	106	96	108	97	94	96
325	86			100	89	92	95
350	72			96	78		73
375	82						76
400							
425							
450							
475							
500							

APPENDIX XIII. Time (seconds) to achieve a 50% rise in baseline periflux (PFU) value in 5 animals at a laser power of 2.0 watts.

Time (secs)	Animal 1 (PFU)	Animal 2 (PFU)	Animal 3 (PFU)	Animal 4 (PFU)	Animal 5 (PFU)
Base PFU	100	100	110	100	80
Target PFU	150	150	155	150	120
25	219	230	282	273	253
50	196	207	310	282	180
75	168	190	220	189	175
100	170	163	195	172	186
125	166	170	172	152	171
150	170	161	185	176	156
175	170	157	176	167	140
200	164	151	163	160	138
225	145	143	151	154	128
250	132		158	142	114
275			143	147	108
300			137		
325					
350					
375					
400					
425					
450					
475					
500					

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