Review

Interstitial laser coagulation for hepatic tumours

J. Heisterkamp, R. van Hillegersberg and J. N. M. IJzermans

Department of Surgery, Erasmus University and University Hospital Rotterdam 'Dijkzigt', Rotterdam, The Netherlands
Correspondence to: Dr J. Heisterkamp, PO Box 2040, NL-3000 CA, Rotterdam, The Netherlands

Background: **The potential role of interstitial laser coagulation (ILC) for patients with irresectable hepatic tumours is currently being investigated. Since its introduction in 1983 it has evolved into an innovative minimally invasive technique.**
Methods: **On the basis of a Medline literature search and the authors' experience, the principles, current state and prospects of ILC for hepatic tumours are reviewed.**
Results: **Animal studies and early clinical studies have shown the safety and feasibility of ILC. The site of interest can be approached at laparoscopy or percutaneously and treatment is easily repeatable. Recent advances include the use of fibres with a cylindrical diffusing light-emitting tip, the length of which is adaptable to tumour diameter, water-cooled fibre systems, simultaneous multiple fibre application, and hepatic inflow occlusion during laser treatment. ILC allows complete destruction of tumours up to 5 cm in diameter. Currently a limitation is the lack of reliable real-time monitoring of laser-induced effects but progress in magnetic resonance imaging techniques should allow accurate temperature measurements to be obtained rapidly during treatment. However, the actual benefit of ILC in terms of patient survival remains to be investigated.**
Conclusion: **In terms of tools and experience, ILC has now been developed sufficiently to study its effect on survival of patients with irresectable hepatic tumours.**

Paper accepted 9 November 1998 British Journal of Surgery 1999, **86**, 293–304

Surgical resection of primary and secondary hepatic tumours leads to an improved 5-year survival rate of 20–40 per cent[1]. The majority of patients with hepatic metastases of colorectal carcinoma, however, do not fulfil the criteria that justify partial hepatectomy[2–4]. Resection of hepatocellular carcinoma (HCC) in cirrhotic liver is restricted even further by the high operative risk associated with the poor general status of the patient and/or the reduced functional hepatic capacity[5]. In the past 10 years the introduction of screening programmes has resulted in a relative increase in the number of resectable cases; the absolute number patients for whom no treatment is available has also increased[5,6].

Alternative therapies have been developed for the treatment of hepatic malignancies, aimed at local, regional or systemic treatment. As segmental and even subsegmental resections may yield results akin to those of larger partial hepatectomies[7–9], provided the resection margin is free from tumour cells, there is a rationale for local tumour destruction. Furthermore, on theoretical grounds, stimulation of dormant malignant cells may be less when using local approaches[10,11]. In general, the various local techniques using physical means (cold, heat or dehydration) lead to instant cell death. Cryosurgery, alcohol injection, radiofrequency coagulation and focused ultrasound are currently being investigated and have been reviewed in recent articles[12–14]. Overall, their widespread clinical application has been hindered by ineffective or unpredictable tumour destruction or by hepatotoxicity[15].

Interstitial laser coagulation (ILC), introduced in 1983 by Bown[16], has matured in recent years. ILC is a thermal technique aimed at coagulation of solid tumours by local light delivery using thin flexible fibre(s) (*Fig. 1*). Early experimental findings have been confirmed in preliminary clinical case series, as reported earlier in this journal[17,18]. While the ILC procedure itself was judged feasible and tolerable, improvement in the technique was necessary for its successful application to tumours larger than 2·5 cm in diameter. In this review the background, recent progress and future perspectives of ILC are discussed with regard to the treatment of hepatic tumours.

© 1999 Blackwell Science Ltd

Methods

A Medline search (OVID Technologies 3.0, New York, USA) was carried out for the period from 1983 to the present using the textwords 'laser', 'liver' and 'interstitial'. Furthermore, relevant papers were identified from the reference lists of the papers previously obtained through the Medline search together with abstracts from recent international meetings. Papers describing clinical studies were included only if (1) the tumour response rates were stated and (2) complications were described.

Laser–tissue interaction

ILC uses laser light at low power (3–15 W) with long exposure times (3–20 min), resulting in coagulation, noted as blanching of the tissue as in a boiled egg (*Fig. 1*). The treated area is left to undergo necrosis *in situ* with subsequent healing by regeneration and/or fibrosis. The volume of tissue destruction is a function of both fibre position(s) within the tumour, and the temperature gradients created by the amount of power and duration of exposure. The subsequent biological response to laser light depends on the interaction of the light with the tissue[19]. On absorption of the laser light several thermal effects occur (*Table 1*). Coagulation is defined as the irreversible thermal damage of tissue proteins at temperatures between 55 and 95°C.

The compromise between deep penetration of the laser light and sufficient absorption in the tissue determines the optimal wavelength for ILC. Neodymium yttrium–aluminium–garnet (Nd YAG) (wavelength 1064 nm) and diode light (890 nm) have been investigated[23–25]. Both wavelengths are minimally absorbed by water and depend on tissue chromophores for their effect. Nd YAG light penetrates the tissue up to 10 mm from the light source[19].

As tumour and liver differ in colour, their optical characteristics might also differ. Van Hillegersberg *et al.*[26] found no net difference in absorption coefficient between rat tumour and liver at 1064 nm; scattering was only slightly greater in tumour. More important are changes in optical characteristics in the process of coagulation (during

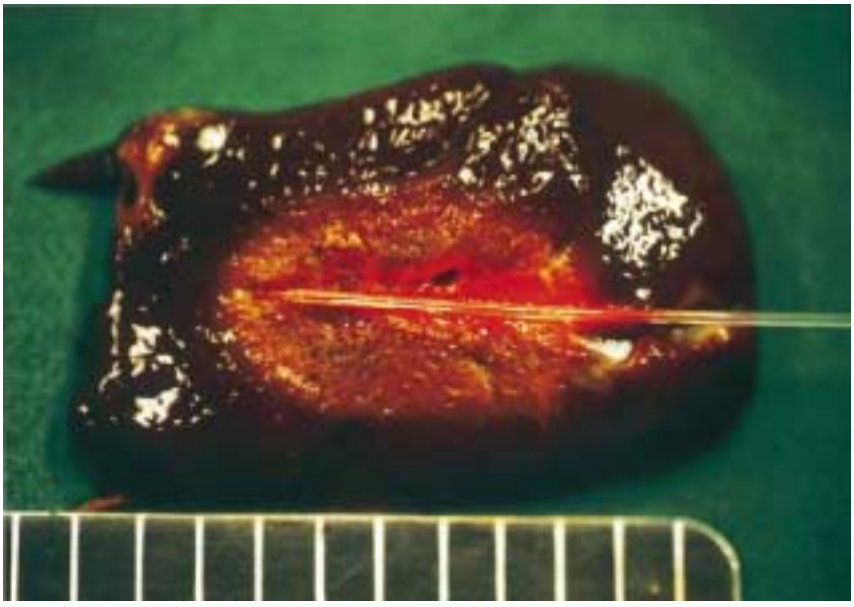

Fig. 1 Coagulated lesion in *ex vivo* pig liver. After laser treatment (6 W during 6 min (2160 J) of neodymium yttrium–aluminium–garnet light) the liver was sectioned in the plane along the laser fibre which is *in situ* (0·9 mm in diameter with a cylindrical diffusing tip of 2 cm). The whitish region is the resulting area of coagulation (maximum length 36 mm, diameter 26 mm)

Table 1 Tissue temperature and effects

Temperature (°C)	Physical effect	Biological effect
40–45	Heating	Enzyme inactivation
60–140	Protein denaturation	Cell shrinkage, hyperchromasia, membrane rupture, pyknosis, hyalinization of collagen
100–300	Water vaporization	Extracellular steam vacuole and cell shrinkage
300–1000	Carbonization and ablation	Ablation vaporization and carbonization

From Thomsen[20], Hunter and Dixon[21] and Welch *et al.*[22]

© 1999 Blackwell Science Ltd

laser treatment). Light measurements during laser treatment of a tumour implanted in rat liver showed that light uptake increased, suggesting that absorption in the coagulated area decreased and light penetration increased[27]. This has recently been confirmed by determination of the optical characteristics of vital and coagulated tissue[28].

Both increasing power and increasing exposure time result in an increase in the area of coagulation; power is the most important factor[29,30]. Eventually, lesion size is limited at a plateau owing to decreased light density and conducted heat at the tissue peripheral to the laser fibre[31].

Interstitial laser fibres

With the use of a conventional bare-tip fibre, where light emission is concentrated at the tip, carbonization occurs. The blackish tissue limits the penetration of light to the surrounding tissue resulting in local temperature accumulation[22]. As a consequence, the temperature profile from a carbonized tip is no different from that of any other type of hot tip; one might as well use a hot knitting needle. With cylindrical diffusing fibre tips homogeneous light emission is produced over the entire light-diffusing length, as seen in *Fig. 1*, allowing the emitted laser light to be distributed equally throughout the surrounding tissue[31]. It was initially thought that carbonization was necessary to create a large lesion[25,30,32]. However, at the optimal combination of exposure time and laser power, light-diffusing tips result in larger lesions with less interlesion variation[29,33]. Recent years have seen major improvements in the quality of the diffusing tip fibres, resulting in better flexibility and thermoresistance. In addition, the length of the diffusing tip can be adapted to tumour diameter[29,34].

As the eventual coagulation size that can be produced with a single fibre is limited, simultaneous multiple fibre application has been used for lesions greater than 2 cm in diameter[35,36]. Owing to a synergistic effect between the fibres, a fourfold to sixfold increase in lesion volume occurs[37], resulting in areas of coagulation 5 cm in diameter[38]. Both reduced heat dissipation in the centre of the fibres and an additive effect at the borders of the individual lesions account for this effect[35]. For this purpose several beam-splitting devices have been developed so that a single laser machine can feed multiple fibres[17,39,40]. In studies in *ex vivo* porcine liver a discrete optimal mutual fibre distance (2 cm) for the maximal synergistic effect was found (lesions with a diameter of 5 cm[38]). The importance of the mutual fibre distance is illustrated by the finding that smaller distances between the fibres resulted in smaller lesions with central carbonization, whereas larger distances resulted in multiple separate zones of coagulation.

The latest development is a closed catheter system, transparent to laser light, through which a diffusing tip is introduced into the tissue[41]. The catheter is irrigated with water during laser treatment. This produces a temperature reduction at the surface of the catheter, allowing the exposure time and power to be increased without the risk of carbonization and fibre destruction. Lesions up to 5 cm in diameter can be created when used in combination with diffusing tips of 4 cm[42]. The insertion of one fibre into a tumour is more precise than the positioning of four fibres at an equal depth and discrete mutual distance. However, as the closed catheter system is larger in diameter (1·6 *versus* 3 mm) flexibility is reduced and the risk of haemorrhage in the tract to the target may be increased.

Histopathological evidence of effect

Thermal protein denaturation results in macroscopic tissue whitening but this is not a good indicator of the exact outer boundary of the lethal tissue effect. Under light microscopy the borders of a coagulated lesion show a rim consisting of haemorrhage, hyperaemia and oedema[43,44]. This haemorrhagic zone is a typical finding after laser coagulation in a variety of tissues and is explained by thermal intravascular erythrolysis[43]. The cells of the zone are devitalized as shown by loss of mitochondrial enzymatic activity[45].

Morphological observations using light microscopy do not allow unambiguous conclusions about the cell viability in coagulated tissue immediately after treatment. Cells with a nucleus have been described in haematoxylin and eosin-stained biopsy specimens following ILC, which were found to be non-vital when studied with electron microscopy[46]. With immunohistochemical methods the authors' group and others have ruled out the presence of vital cells in animal models with and without tumour, using either localization of nicotinamide adenine dinucleotide metabolism directly after ILC treatment[45,47] or by 5-bromo-2′-deoxyuridine incorporation 6–36 days after ILC (*Fig. 2*)[27,48]. Complete cell death has also been confirmed in laser-induced coagulation in the resection specimens of patients with hepatic metastases who underwent resection 2–3 days after ILC[49].

Notwithstanding the difficulties in defining coagulation damage, a rough outline can be given. In essence, no difference in reaction between tumour and normal tissue has been found. The acute lesion has a characteristic zonal architecture as described in detail in the literature[27,50,51]. Briefly, in a central zone surrounding the insertion of the laser probe the gross tissue structure is well preserved, whereas cellular build-up is characterized by acidophilic

© 1999 Blackwell Science Ltd

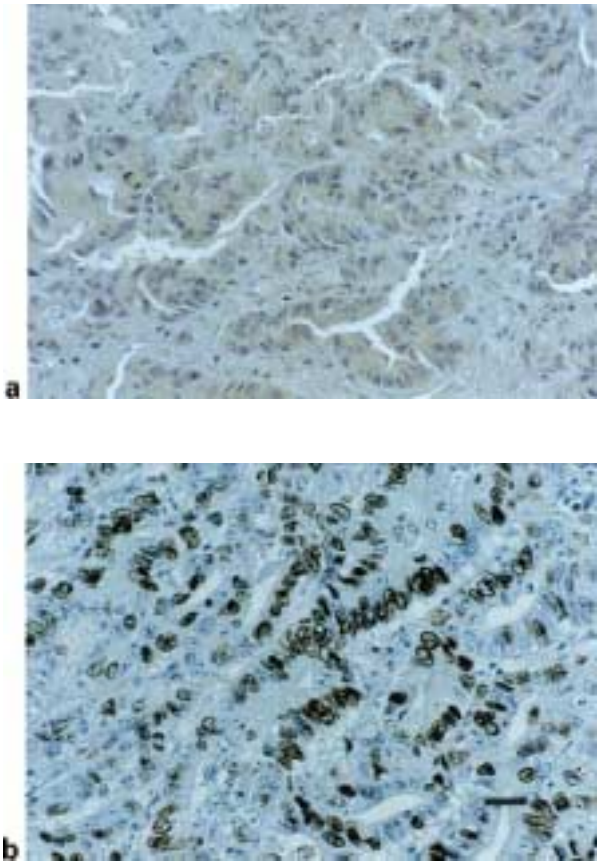

Fig. 2 5-Bromo-2′-deoxyuridine (BrdU) histochemistry of CC531 tumour in rat liver 36 days after laser or sham treatment. **a** The nuclei of the coagulated tumour in the degenerative core do not label with anti-BrdU, a marker of proliferating DNA. **b** Strong labelling in the cellular nuclei of a tumour in a sham-treated animal (bar 15 μm). Haematoxylin and eosin stain. (Reproduced with permission from R. van Hillegersberg. Laser treatment for hepatic metastases: thermal and photodynamic therapy. *Thesis*, Erasmus University, Rotterdam, 1993)

cytoplasm and elongated nuclei (*Fig. 2a*). In liver tissue this zone is surrounded by a broad area, containing dilated sinusoids and cells with vacuolated cytoplasm. The outer, macroscopically detectable, haemorrhagic zone consists of cells with less vacuolated cytoplasm and hyperaemic sinusoids.

In the process of regeneration, a fibrotic rim is formed delineating normal tissue from the coagulum, which can be palpated as a dense mass. This process of regeneration is a mesenchymal reorganization with proliferation of fibroblasts, endothelium and bile ducts[17,27,52,53]. The original tissue architecture remains intact with no ingrowth of blood vessels inside the fibrotic rim. Depending on initial size, complete regeneration of hepatic tissue takes place between 3 and 12 months after laser treatment, as demonstrated in normal liver of rabbits[52], dogs[17] and pigs[53].

Studies in experimental animal models

Studies in animal models have been performed using tumour-bearing rodents[27,54] and rabbits[55,56], as well as in rodents[57,58], dogs[17] and pigs[44,45,48,59–61] with normal livers. In the tumour models the cytotoxicity of ILC was studied; the normal-liver models allowed strategies to increase coagulation volume at human scale to be investigated.

The earliest documented work was by Matthewson *et al.*[62] in rat liver using Nd YAG light. A 0·4-mm diameter fibre was inserted into the centre of a lobe of liver, exposed at laparotomy. Power settings of 0·5–2 W and exposure times of 50–2400 s were used to give well defined lesions of coagulative necrosis with sharp boundaries between normal and coagulated liver. The size of coagulation increased with increasing laser energy until a plateau was reached. Van Hillegersberg *et al.*[27] studied ILC in a rat liver tumour model. Lesion size and liver enzymes increased with laser energy applied. Deterioration in liver function was not found. At optimal laser settings complete tumour eradication was obtained. In addition, several rodent models with subcutaneous implanted tumours showed the tumour cell killing potential of ILC[63,64]. Recently an indication of reduced outgrowth of remnant tumour has been found after ILC compared with resection in liver tumours in rats[65].

In a second phase of animal experiments, modifications to enlarge the volume of coagulation were studied in large-animal models. Steger *et al.*[17] used dogs to evaluate the use of a laser beam-splitting device to feed four fibres at a mutual distance of 1·5 cm which resulted in lesions of 3·5 cm maximum.

A second line of investigation was to evaluate the influence of hepatic blood flow on the magnitude of the coagulation. Computer simulations[66] and mathematical modelling[67] predicted a fourfold to fivefold increase in the area of coagulation in liver without blood flow. The relatively small size of previous animal models and the small volume of coagulation that could be produced had obscured such an effect. These predictions were confirmed independently by three research groups, using multiple[44,45] and single[48] fibre application in pigs. With physiological blood flow through the liver, the volume of coagulation is reduced to 10–20 per cent and tissue is preserved around large vessels[52,68]. Germer *et al.*[45] and Möller *et al.*[48] investigated complete occlusion *versus* physiological flow, and the authors' group also differen-

© 1999 Blackwell Science Ltd

tiated between portal inflow occlusion only *versus* complete inflow occlusion (arterial and portal). It was found that portal inflow occlusion suffices to overcome the cooling effect of the blood flow[44]. Although it is generally assumed that hepatic metastases are mainly supplied by the arterial tree[69], clamping of both hepatic artery and portal vein is unlikely to be needed in the clinical situation. The poorly organized vascular bed in the tumour will probably cause only minimal tissue cooling and thus minimal lesion reduction[70]. Furthermore, in the often ischaemic centre of the tumour, in particular, little extra effect can be expected from eliminating the arterial blood flow. However, the tumour is surrounded by well perfused liver parenchyma and it is here that the cooling effect is mainly exerted[71]. Therefore, eliminating portal blood flow should enhance the destruction of the vital rim of the tumour and a margin of normal liver tissue. Also portal inflow occlusion alone, through a percutaneous transhepatic route[72,73], is less invasive than methods of achieving total arrest of blood flow. In a recent experimental study in pigs, the authors investigated the effects of ILC in the liver with portal inflow occlusion with a long-term follow-up[53]. No adverse events occurred, even in the vicinity of large vessels situated centrally in the liver. For ILC of primary liver cancer, portal inflow occlusion may not be needed in a cirrhotic liver, as the portal flow is often negligible or even retrograde. In this situation the magnitude of the arterial flow should be considered as a potential cooling source.

Treatment monitoring and evaluation

Currently, ILC is limited by the lack of reliable real-time monitoring of laser-induced effects. Ideally, real-time monitoring of ILC should provide information about the extent of coagulation in relation to the anatomy of the liver during treatment. The intervention may then be prolonged to ensure complete coagulation of the entire tumour, or terminated to prevent damage to vital structures. Interstitially placed thermosensors and light detectors for precise measurements are of little use because of the limited number of sample points and the extra trauma associated with their placement. It is likely that real-time monitoring by a non-invasive imaging technique is the key to control ILC. Several such techniques have been investigated.

Ultrasonography

Ultrasonography enables accurate placement of catheters into the tumour. Real-time imaging of the treated area has also been investigated but the echogenic area that is observed during coagulation does not correlate with the coagulative damage[48,74,75]. The image is caused by formation of bubbles from evaporated tissue water. Ultrasonography is also not helpful in evaluating lesions after treatment as the echogenic area becomes heterogeneous within minutes[75,76].

Computed tomography

For the diagnostic assessment before treatment, triphasic spiral computed tomography (CT) is indicated to define the number, location and dimensions of metastases before therapy. Contrast-enhanced CT after treatment shows the result of laser treatment very clearly as a well defined, non-enhanced area, easily distinguishable from the untreated, thus vascularized, enhancing tumour areas (*Fig. 3*). Contrast-enhanced triphasic CT after laser treatment should be considered as the evaluative 'gold standard'. The optimal time to perform ILC after CT is between 1 and 4 days, which corresponds with the time at which experimentally induced coagulated lesions have their maximum diameter. Unfortunately, after longer intervals CT cannot differentiate between inflammatory change, regenerating liver or recurrent tumour. Because of the radiographic load and insensitivity to soft tissue changes, there is no role for real-time CT during ILC.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) is not restricted solely to morphology; physiological parameters may also be measured. Initial experience in monitoring laser treatment in patients with hepatic metastases consisted of conventional T1-weighted imaging[77–79]. These T1-weighted sequences are available on all clinical systems and do not require advanced computer-assisted image interpretation. The temperature dependence of T1 has been demonstrated *in vitro* for several biological systems[80]. However, the relationship between T1 and temperature is not simple because of the multifactorial nature of T1[81,82]; the temperature dependence of T1 also varies strongly for different types of tissue[81]. Furthermore, precise measurements of the absolute value of T1 are difficult[83]. Gewiese *et al.*[84] visualized a laser heated region, in *ex vivo* tissue, as a bright area surrounded by a dark border which was found to correspond with an isotherm of 45°C (20°C increase from starting temperature). More subtle differences, however, were undetectable. Therefore the current status of T1-weighted monitoring of heat deposition in tissue does not represent adequate thermometry.

The change in the proton resonance frequency (PRF) represents an alternative temperature-dependent magnetic

© 1999 Blackwell Science Ltd

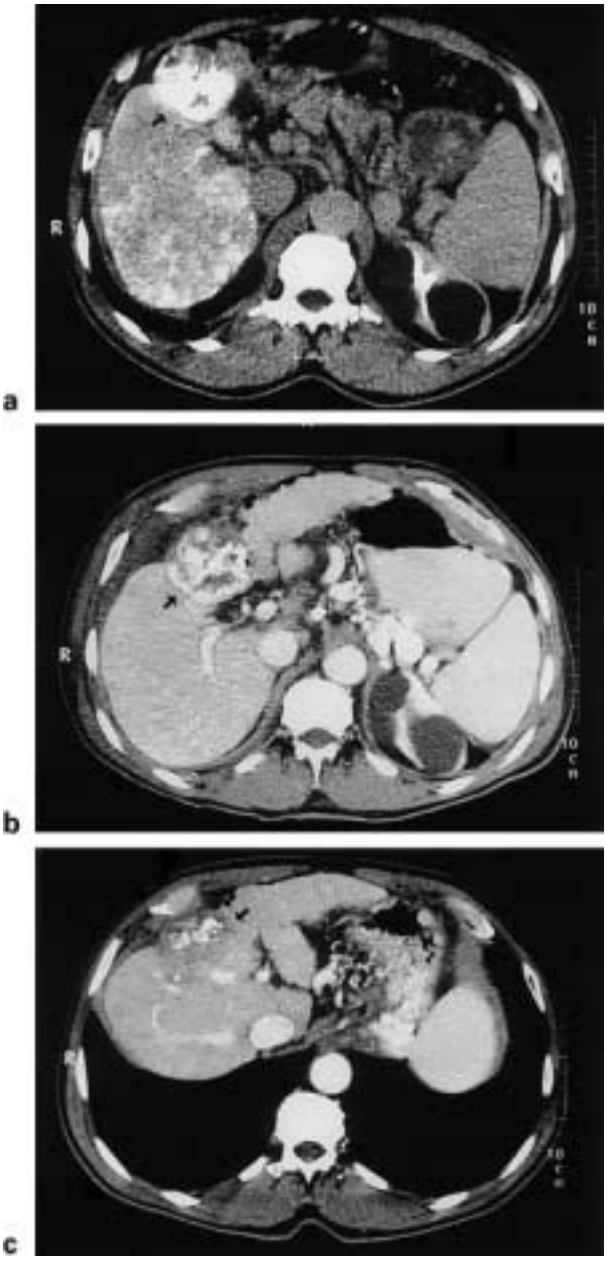

Fig. 3 Contrast-enhanced computed tomogram **a** before, **b** 1 day after and **c** 7 months after laser treatment of a 4·5-cm large hepatocellular carcinoma in the anterior sector of segment four (arrow). Because of cirrhosis, portal flow was negligible during treatment (four fibres with diffusing tips of 5 cm). Through these fibres 12·5 W of neodymium yttrium–aluminium–garnet light per fibre was guided simultaneously over 6 min (4500 J per fibre). In **b** and **c** laser-induced avascularity is seen. In **c** a small enhancing rim (double arrow) indicates incomplete tumour destruction (a second laser treatment was scheduled)

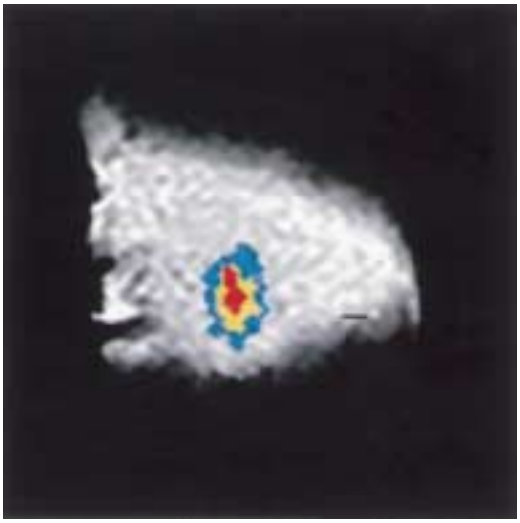

Fig. 4 Magnetic resonance image showing a transverse slice of liver lobe (*ex vivo*) scanned in dynamic series during laser treatment with a single fibre (cylindrical diffusing tip of 2 cm) with 6 W over 6 min. Temperatures were calculated relative to the baseline proton resonance frequency in a reference scan before treatment[90]. Colour overlays, over the baseline morphological image, represent temperature increases compared with those at the start of the experiment (32°C in this particular case): + 8°C (blue), + 18°C (yellow) and + 28°C (red). Temperatures could be determined with an accuracy of ± 3·5 s after 6 min of laser application (95 per cent confidence interval). Correlation between the dimensions of macroscopic coagulation and the largest diameters of the 60°C isotherm was 0·94. Bar indicates 1 cm

resonance variable. The PRF method provides a direct estimate of temperature changes[85], and the feasibility and accuracy of this subtraction technique was demonstrated in 1995[86,87]. In *ex vivo* and *in vitro* models the accuracy of phase-shift mapping was within 4°C[85,88,89] (*Fig. 4*). Respiration-induced artefacts do not result in a decreased accuracy[90]. Currently this technique is under investigation in preclinical models.

For MRI assessment after treatment both T1- and T2-weighted scans have been proposed[91,92]. With sophisticated T1-weighted scans the area of coagulation at the end of treatment could be predicted very accurately. This was investigated in animal models[47,93] and in surgical candidates who underwent resection 2–3 days after MRI-guided laser treatment[49,94] (allowing correlation between MRI and histopathology). In a recent study these encouraging findings were compared with CT, considered as the gold standard, for validation[95]. A good correlation was found between the MRI scan at the end of laser application and the CT scan at 24 h. Currently, space to access the patient is limited in high-field MRI machines; progress in this field

© 1999 Blackwell Science Ltd

and the development of magnetic resonance-compatible equipment promises future high-field MRI with the capacity for intervention from all sides[96,97].

Clinical experience

The cumulative clinical experience is summarized in *Table 2*. The first clinical report came from Hashimoto *et al.*[104] in 1985 who treated patients with liver metastases and HCC at laparotomy. A Nd YAG laser at a low power output of 5 W was used with a relatively long exposure time and a bare-tip laser fibre was employed. From this study it appeared that the technique could be performed without major complications. A drop in tumour marker levels was recorded, but the benefit to patients remained unclear. In later studies the technique was improved using various combinations of power output and exposure times, and adaptation of the fibre tip to avoid carbonization. Hahl *et al.*[105] and Huang *et al.*[106] actually used hyperthermia, instead of direct coagulation, which means that the temperature was held between 41 and 45°C over 10–30 min. A fatal complication was caused by air emboli as a result of interstitial air introduced for cooling of the fibre tip, a method of cooling that has been abandoned ever since.

The percutaneous procedure was introduced by Steger *et al.*[107] and later adapted by Nolsoe *et al.*[99] and Schroder *et al.*[100]. Total eradication of small tumours was described. Failures were noted mostly for lesions larger than 2·3 cm; this threshold for a complete response was also found in a larger series by Vogl *et al.*[77] using single fibre application with a diffusing tip in a percutaneous procedure. In sequel

Table 2 Review of clinical interstitial laser coagulation of hepatic maligancies with emphasis on the treatment response at 6 months

a

Reference	Year	Group characteristics*	Technique	Approach†
Huang *et al.*[106]	1991	7 HCC (2–4 cm)	Diffusing tip; 2–3 W, 20–30 min	Laparotomy (thermocouple)
Nolsoe *et al.*[99]	1993	16 CRCs (1–4 cm)	Diffusing tip; 4–8 W, 5–45 min	Laparotomy 2 (thermocouple), percutaneous 9 (US)
Amin *et al.*[76]	1993	34 CRCs, 21 secondaries of mixed origin (1–15 cm)	4 × bare tips simultaneously; 2 W, 7 min	Percutaneous (US)
Schroder *et al.*[100]	1994	2 HCC (3–7 cm); 2 breast secondaries, 6 CRCs (0·5–7 cm)	Bare tip; 2–6 W, 8–15 min	Laparotomy (US)
Dowlatshahi *et al.*[101]	1995	45 lesions in 20 patients; HCC and CRCs	Bare tip; 5–10 W, 7 min	Laparotomy (US)
Tranberg *et al.*[102]	1996	3 HCC, 18 CRCs, 1 pancreatic secondary (1–10 cm)	Frosted sapphire tip; 6–10 W, 5 min with complete hepatic inflow occlusion	Laparotomy (US)
Gillams *et al.*[103]	1997	148 secondaries in 55 patients (1–6 cm)	2 × 4 bare tips simultaneously; 2 W per fibre, 7 min	Percutaneous (US and MRI)
Vogl *et al.*[79]	1997	282 CRCs in 99 patients (< 5 cm)	Diffusing tip; 10 W, 10–20 min	Percutaneous (MRI)

*Values in parentheses are tumour diameters. †Monitoring technique is shown in parentheses.

b

Reference	Year	Tumour response at 6 months	Mean (range) no. of treatments	Complications
Huang *et al.*[106]	1991	CT: 40% CR, 40% PD	1·1 (1–2)	Mild pain
Nolsoe *et al.*[99]	1993	US: 75% CR (mean 2·4 cm), 25% SD (mean 3·4 cm)	1 only	Mild pain, temperature increase, pleural effusion
Amin *et al.*[76]	1993	CT: 38% CR, 44% SD; failures at > 4 cm in diameter	3·2 (1–8)	Severe pain, subcapsular haematoma, pleural effusion, temperature increase
Schroder *et al.*[100]	1994	CT: 8% CR, 58% SD, 33% PD	1·8 (1–4)	Biloma, vasovagal reaction, shoulder pain
Dowlatshahi *et al.*[101]	1995	CT: 68% CR (< 2·5 cm); 0% CR (> 2·5 cm)	1 only	n.s.
Tranberg *et al.*[102]	1996	CT: 16% CR, 38% PR, 46% SD/PD	1 only	1 fatal multiple organ failure
Gillams *et al.*[103]	1997	CT: 15% CR, 38% PD	2·2 (1–12)	n.s.
Vogl *et al.*[79]	1997	MRI: cumulative 3-year survival rate 42%	8 (1–36)	Nausea, right subphrenic haemorrhage

HCC, hepatocellular carcinoma; CRCs, colorectal cancer secondaries; CT, computed tomography; US, ultrasonography; MRI, magnetic resonance imaging; CR, complete response; PD, progressive disease; SD, stable disease; PR, partial response; n.s., not stated

© 1999 Blackwell Science Ltd

to Steger's study, Amin *et al.*[76] used a method of bare-tip fibre application which required reinsertion and repulling of the fibres to cover the tumour completely. Tranberg *et al.*[102] treated patients at laparotomy with complete hepatic inflow occlusion and from one to four fibres according to tumour size.

Complications

Minor complications such as pain at the fibre insertion site, pleural effusion, local (subcapsular) haematoma, and pain at the shoulder as a result of diaphragmatic irritation, occur in approximately 90, 10, 10 and 15 per cent of patients respectively. The subfebrile temperatures after treatment, reported in several series, may be due to the presence of necrotic tissue in the liver or a sterile peritonitis at the fibre insertion site. That the procedure is fairly easily tolerated is illustrated by the percutaneous protocols in which the patients are usually discharged 24 h after treatment with minimal requirement for analgesia.

Serious complications in the series without flow occlusion are seldom encountered; bilomas or haemorrhages requiring external drainage have not yet been reported. One case of fatal Budd–Chiari syndrome occurred on the day after laser treatment in a patient in London (S. G. Bown, personal communication), emphasizing the need for accurate monitoring of laser-induced effects near vital intrahepatic structures such as the hepatic veins. Tranberg *et al.*[102] reported a death from multiple organ failure due to massive tumour necrosis after laser treatment of an 8-cm lesion. In their series complete occlusion of hepatic flow was applied. The situation may be compared with the 'cryoshock phenomenon' in which multiple organ failure ensued after treating large tumours with cryosurgery[108]. There are no reports of injury to major vascular or biliary structures after ILC close to major portal pedicles with hepatic inflow occlusion, and so such siting is not considered as a contraindication to treatment. In the authors' clinical experience, ILC with portal inflow occlusion of tumours up to 4·5 cm in diameter has always been safe and tolerable.

Outcome

As each study defines its own criteria of selection and evaluation, the outcomes in terms of tumour response and survival are difficult to compare (*Table 2*). In an updated series, Vogl *et al.*[79] evaluated the effect on survival after percutaneous ILC in 99 patients with colorectal metastases of the liver. A 3-year survival rate of 42 per cent with a median survival of 36 months was reported (88 per cent at 1 year). This was at the expense of an average of 2·9 repeated treatments per tumour (range not stated), both for recurrence in treated tumours and for newly diagnosed tumours (not distinguished). In the cumulated London series mean survival was 18 months in 44 patients with an mean number of 2·2 repeated treatments; the 1-year survival rate was 87 per cent[103]. For patients treated at laparotomy, results were less favourable, possibly because of the larger diameters of the treated tumours (up to 10 cm)[102]. Median survival after treatment was 8·5 months and this was mainly influenced by recurrent disease at various extrahepatic sites (in 70 per cent of patients). Recently the first significant series of ILC in patients with HCC was reported; in 12 patients 17 lesions were treated and median survival was 34 months[109]. Currently, in the percutaneous protocols the number of tumours is limited to five and the diameter to 5 cm.

Procedural considerations

ILC can be performed percutaneously under intravenous sedation and analgesia, allowing a short hospital stay with 24-h observation after treatment. On the other hand, general anaesthesia with artificial ventilation results in better respiratory control for respiratory triggered real-time MRI scanning, prevents patient discomfort and movement during treatment, and renders portal inflow occlusion more tolerable. In the authors' experience and as reported by others percutaneous transhepatic catheterization and balloon occlusion of the portal vein can be performed safely by an experienced interventional radiologist[72,73,110]. For lesions high in the hepatic dome, transthoracic and transdiaphragmatic fibre insertion may be necessary. For lesions located in the left hemiliver a subcostal route is feasible, whereas for right-sided tumours insertion in the intercostal space may be considered to avoid vital structures, especially when inserting multiple fibres. An advantage of percutaneous treatment is the feasibility of repeated treatment.

There are also advantages of an open or laparoscopic approach[45,111]. Fibre positioning under direct view may be more reliable, resulting in complete tumour destruction in a single treatment session. Intraperitoneal tumour deposits, making the laser treatment pointless, can be detected at laparotomy or laparoscopy. Needle tract haemorrhage is detected instantly and can be treated under direct vision. The liver can be mobilized allowing access to lesions located posteriorly[112] and, finally, for deep-seated lesions more flexibility is created in choice of the insertion tract. In pigs, laparoscopic ILC has been combined with real-time MRI monitoring in an open interventional magnetic resonance scanner[111]. In this way

 © 1999 Blackwell Science Ltd

the precision of positioning under direct view is combined with reliable interstitial monitoring.

Conclusion

ILC is one of the modalities under current investigation for local control of hepatic malignancies. In this review the principles underlying ILC have been discussed. From the results of animal and clinical studies it may be concluded that ILC is safe and feasible using either a laparoscopic approach or percutaneous access. Recent advances are the use of fibres with a cylindrical diffusing light-emitting tip of which the length is adaptable to tumour diameter, water-cooled fibre systems, simultaneous multiple fibre application, and hepatic inflow occlusion during laser treatment. Complete destruction of tumours up to 5 cm in diameter can be realized. In the light of recent developments allowing accurate real-time monitoring with MRI, the authors are optimistic about the role of ILC in the management of hepatic malignancies. Although ILC for hepatic tumours should still be regarded as an experimental treatment[15], it is legitimate to evaluate its impact on the survival of patients with irresectable hepatic tumours. When the accuracy and efficiacy of ILC has been established unequivocally, comparison with surgical resection in controlled clinical trials will be justified.

References

1 Taylor I. Liver metastases from colorectal cancer: lessons from past and present clinical studies. *Br J Surg* 1996; **83:** 456–60.

2 Herfarth C, Kallinowski F. Can clinical assessment predict a patient's prognosis after liver metastasis? *Ann Surg* 1997; **226:** 581 (Editorial).

3 Wanebo HJ, Chu QD, Vezeridis MP, Soderberg C. Patient selection for hepatic resection of colorectal metastases. *Arch Surg* 1996; **131:** 322–9.

4 King's Fund Forum. Cancer of the colon and rectum (consensus statement). *Br J Surg* 1990; **77:** 1063–5.

5 Akriviadis EA, Llovet JM, Efremidis SC, Shouval D, Canelo R, Ringe B *et al.* Hepatocellular carcinoma. *Br J Surg* 1998; **85:** 1319–31.

6 IJzermans JN, Bac DJ. Recent developments in screening, diagnosis and surgical treatment of hepatocellular carcinoma. *Scand J Gastroenterol Suppl* 1997; **223:** 50–4.

7 Nordlinger B, Guiguet M, Vaillant JC, Balladur P, Boudjema K, Bachellier P *et al.* Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Association Française de Chirurgie. *Cancer* 1996; **77:** 1254–62.

8 Rees M, Plant G, Bygrave S. Late results justify resection for multiple hepatic metastases from colorectal cancer. *Br J Surg* 1997; **84:** 1136–40.

9 Nagasue N, Yukaya H, Ogawa Y, Hirose S, Okita M. Segmental and subsegmental resections of the cirrhotic liver under hepatic inflow and outflow occlusion. *Br J Surg* 1985; **72:** 565–8.

10 Gutman M, Fidler IJ. Biology of human colon cancer metastasis. *World J Surg* 1995; **19:** 226–34.

11 Slooter GD, Marquet RL, Jeekel J, IJzermans JNM. Tumour growth stimulation after partial hepatectomy can be reduced by treatment with tumour necrosis factor α. *Br J Surg* 1995; **82:** 129–32.

12 Scudamore CH, Patterson EJ, Shapiro AM, Buczkowski AK. Liver tumor ablation techniques. *J Invest Surg* 1997; **10:** 157–64.

13 de Sanctis JT, Goldberg SN, Mueller PR. Percutaneous treatment of hepatic neoplasms. A review of current techniques. *Cardiovasc Intervent Radiol* 1998; **21:** 273–96.

14 Cascinu S, Del Ferro E, Grianti C, Ligi M, Ghiselli R, Foglietti G *et al.* Inhibition of tumor cell kinetics and serum insulin growth factor I levels by octreotide in colorectal cancer patients. *Gastroenterology* 1997; **113:** 767–72.

15 Consensus Statement. Treatment of hepatic metastases from colorectal cancer. *Journal of Gastrointestinal Surgery* 1997; **1:** 396–7.

16 Bown SG. Phototherapy in tumors. *World J Surg* 1983; **7:** 700–9.

17 Steger AC, Lees WR, Shorvon P, Walmsley K, Bown SG. Multiple-fibre low-power interstitial laser hyperthermia: studies in the normal liver. *Br J Surg* 1992; **79:** 139–45.

18 Masters A, Steger AC, Bown SG. Role of interstitial therapy in the treatment of liver cancer. *Br J Surg* 1991; **78:** 518–23.

19 van Hillegersberg R. Fundamentals of laser surgery. *Eur J Surg* 1997; **163:** 3–12.

20 Thomsen S. Pathologic analysis of photothermal and photomechanical effects of laser–tissue interactions. *Photochem Photobiol* 1991; **53:** 825–35.

21 Hunter JG, Dixon JA. Lasers in cardiovascular surgery: current status. *West J Med* 1985; **142:** 506–10.

22 Welch AJ, Motamedi M, Rastegar S, LeCarpentier GL, Jansen D. Laser thermal ablation. *Photochem Photobiol* 1991; **53:** 815–23.

23 Prapavat V, Roggan A, Walter J, Beuthan J, Klingbeil U, Muller G. *In vitro* studies and computer simulations to assess the use of a diode laser (850 nm) for laser-induced thermotherapy (LITT). *Lasers Surg Med* 1996; **18:** 22–33.

24 Mesecke von Rheinbaben I, Roggan A, Muller GJ. *In-vitro* investigations to compare various wavelengths for laser-induced interstitial thermotherapy. In: Altshuler GB, Chiesa F, Geschwind HJ, Hibst R, Krasner N, Laffite F, eds. *Laser Applications in Medicine and Dentistry (Proc SPIE 2922).* Bellingham, Washington: SPIE, 1996: 334–41.

25 Amin Z, Buonaccorsi G, Mills T, Harries S, Lees WR, Bown SG. Interstitial laser photocoagulation: evaluation of a 1320 nm Nd–YAG and a 805 nm diode laser: the significance of charring and the value of pre-charring the fibretip. *Lasers Med Sci* 1993; **8:** 113–20.

© 1999 Blackwell Science Ltd

26 van Hillegersberg R, Pickering JW, Aalders M, Beek JF. Optical properties of rat liver and tumor at 633 nm and 1064 nm: photofrin enhances scattering. *Lasers Surg Med* 1993; **13:** 31–9.

27 van Hillegersberg R, van Staveren HJ, Kort WJ, Zondervan PE, Terpstra OT. Interstitial Nd : YAG laser coagulation with a cylindrical diffusing fiber tip in experimental liver metastases. *Lasers Surg Med* 1994; **14:** 124–38.

28 Ritz JP, Roggan A, Germer CT, Albrecht D, Buhr HJ. Determination of optical parameters of human liver tissue and liver metastases for irradiation planning by laser-induced thermotherapy of liver metastases. *Langenbecks Arch Chir Suppl Kongressbd* 1997; **114:** 335–8.

29 Heisterkamp J, van Hillegersberg R, Sinofsky EL, IJzermans JNM. Heat resistant cylindrical diffuser for interstitial laser coagulation: comparison with the bare-fiber in a porcine liver model. *Lasers Surg Med* 1997; **20:** 304–9.

30 Sturesson C. Interstitial laser-induced thermotherapy: influence of carbonization on lesion size. *Lasers Surg Med* 1998; **22:** 51–7.

31 Svaasand LO, Gomer CJ, Morinelli E. On the physical rationale of laser induced hyperthermia. *Lasers Med Sci* 1990; **5:** 121–7.

32 Wyman DR, Whelan WM, Wilson BC. Interstitial laser photocoagulation: Nd : YAG 1064 nm optical fiber source compared to point heat source. *Lasers Surg Med* 1992; **12:** 659–64.

33 Möller PH, Lindberg L, Henriksson PH, Persson BRR, Tranberg K-G. Interstitial laser thermotherapy: comparison between bare fibre and sapphire probe. *Lasers Med Sci* 1996; **10:** 193–200.

34 Murrer LH, Marijnissen JP, Star WM. Improvements in the design of linear diffusers for photodynamic therapy. *Phys Med Biol* 1997; **42:** 1461–4.

35 Wyman DR. Selecting source locations in multifiber interstitial laser photocoagulation. *Lasers Surg Med* 1993; **13:** 656–63.

36 Davis M, Dowden J, Steger AC, Kapadia P, Whiting P. A mathematical model for interstitial laser treatment of tumours using four fibers. *Lasers in Medical Science* 1989; **4:** 41–53.

37 Ivarsson K, Olsrud J, Sturesson C, Moller PH, Persson BR, Tranberg KG. Feedback interstitial diode laser (805 nm) thermotherapy system: *ex vivo* evaluation and mathemical modeling with one and four-fibers. *Lasers Surg Med* 1998; **22:** 86–96.

38 Heisterkamp J, van Hillegersberg R, Sinofsky EL, IJzermans JNM. Interstitial Nd : YAG laser coagulation using simultaneous multiple fiber application with an optical beamsplitter: the importance of mutual fiber distance. In: Anderson RR, ed. *Lasers in Surgery: Advanced Characteristics, Therapeutics and Systems VII.* Bellingham, Washington: SPIE, 1997: 522–5.

39 Bosman S. Thermal effects of laser light on tissue structure. *Thesis/Dissertation*, University of Amsterdam, 1993.

40 Frank F, Hessel S. Technical prerequisites for the interstitial thermotherapy with the Nd : YAG laser. *Lasermedizin* 1990; **1:** 36–40.

41 Roggan A, Albrecht D, Berlien HP. Application equipment for intraoperative and percutaneous laser-induced interstitial thermotherapy (LITT). In: Roggan A, Muller G, eds. *Laser-induced Interstitial Thermotherapy.* Bellingham, Washington: SPIE, 1995: RvH.

42 Orth K, Russ D, Duerr J, Hibst R, Steiner R, Beger HG. Thermo-controlled device for inducing deep coagulation in the liver with the Nd : YAG laser. *Lasers Surg Med* 1997; **20:** 149–56.

43 Thomsen S. Identification of lethal thermal injury at the time of photothermal treatment. In: Roggan A, Muller G, eds. *Laser-Induced Interstitial Thermotherapy.* Bellingham, Washington: SPIE, 1995: 459–67.

44 Heisterkamp J, van Hillegersberg R, Mulder PGH, Sinofsky EL, IJzermans JNM. The importance of eliminating portal flow in producing large intra-hepatic lesions with interstitial laser coagulation. *Br J Surg* 1997; **84:** 1245–9.

45 Germer CT, Albrecht D, Roggan A, Isbert C, Buhr HJ. Experimental study of laparoscopic laser-induced thermotherapy for liver tumours. *Br J Surg* 1997; **84:** 317–20.

46 Nolsoe CP, Torp-Pedersen S, Horn T, Larson LG, Lorentzen T, Holm HH. Interstitial laser ablation of tumors – follow up biopsies implies a risk of misinterpretation. *Lasers Surg Med* 1989; **18:** 21 (Abstract).

47 Roberts HR, Paley M, Sams VR *et al.* Magnetic resonance imaging of interstitial photocoagulation of normal rat liver: imaging–histopathological correlation. *Minimally Invasive Therapy and Allied Technologies* 1997; **6:** 41–52.

48 Möller PH, Hannesson P, Ivarsson K, Olsrud J, Stenram U, Tranberg KG. Interstitial laser thermotharapy in pig liver: effect of inflow occlusion on extent of necrosis and ultrasound image. *Hepatogastroenterology* 1997; **44:** 1302–11.

49 Vogl TJ, Weinhold N, Muller P, Phillip C, Roggan A, Mack MG *et al.* Early clinical experiences with MR-guided laser-induced thermotherapy (LITT) of liver metastases in preoperative care. *Rofo Fortschr Geb Rontgenstr Neuen Bildgeb Verfahr* 1996; **164:** 413–21.

50 Tracz RA, Wyman DR, Little PB, Towner RA, Stewart WA, Schatz SW *et al.* Comparison of magnetic resonance images and the histopathological findings of lesions induced by interstitial laser photocoagulation in the brain. *Lasers Surg Med* 1993; **13:** 45–54.

51 Schober R, Bettag M, Sabel M, Ulrich F, Hessel S. Fine structure of zonal changes in experimental Nd : YAG laser-induced interstitial hyperthermia. *Lasers Surg Med* 1993; **13:** 234–41.

52 Isbert CM, Germer CT, Albrecht D *et al.* Laser-induced thermotherapy (LITT) for the treatment of liver metastases – the correlation of Gd-DTPA-enhanced magnetic resonance imaging (MRI) and histomorphological findings in the chronic model. In: Anderson RR, ed. *Lasers in Surgery: Advanced Characteristics, Therapeutics and Systems VII.* Proc of SPIE 2970 ed. Bellingham, Washington: SPIE, 1997: 543–53.

 © 1999 Blackwell Science Ltd

53 Heisterkamp J, van Hillegersberg R, Zondervan PE, IJzermans JN. Long term effects of interstitial laser coagulation with portal inflow occlusion in porcine liver: central *versus* peripheral lesions. (in press).

54 Möller PH, Ivarsson K, Stenram U, Radnell M, Tranberg KG. Interstitial laser thermotherapy of adenocarcinoma transplanted into rat liver. *Eur J Surg* 1997; **163:** 861–70.

55 Prudhomme M, Rouy S, Tang G *et al.* Partial response to laser-induced thermotherapy: incidence of biliary structures. In: Altshuler GB, Chiesa F, Geschwind HJ, Hibst R, Krasner N, Laffite F, eds. *Laser Applications in Medicine and Dentistry (Proc SPIE 2922).* Bellingham, Washington: SPIE, 1996: 362–5.

56 Hoye RC, Thomas LB, Riggle GC, Ketcham A. Effects of neodymium laser on normal liver and Vx2 carcinoma transplanted into the liver of experimental animals. *J Natl Cancer Inst* 1968; **41:** 1071–82.

57 Amin Z, Thurrell W, Spencer GM, Harries SA, Grant WE, Bown SG *et al.* Computed tomography–pathologic assessment of laser-induced necrosis in rat liver. *Invest Radiol* 1993; **28:** 1148–54.

58 Matsumoto R, Selig AM, Colucci VM, Jolesz FA. Interstitial Nd : YAG laser ablation in normal rabbit liver: trial to maximize the size of laser-induced lesions. *Lasers Surg Med* 1992; **12:** 650–8.

59 Malone DE, Wyman DR, DeNardi FG, McGrath FP, De Gara CJ, Wilson BC. Hepatic interstitial laser photocoagulation. An investigation of the relationship between acute thermal lesions and their sonographic images. *Invest Radiol* 1994; **29:** 915–21.

60 Dachman AH, McGehee JA, Beam TE, Burris JA, Powell DA. US-guided percutaneous laser ablation of liver tissue in a chronic pig model. *Radiology* 1990; **176:** 129–33.

61 Bosman S, Phoa SS, Bosma A, van Gemert MJ. Effect of percutaneous interstitial thermal laser on normal liver of pigs: sonographic and histopathological correlations. *Br J Surg* 1991; **78:** 572–5.

62 Matthewson K, Coleridge-Smith P, O'Sullivan JP, Northfield TC, Bown SG. Biological effects of intrahepatic neodymium : yttrium–aluminum–garnet laser photocoagulation in rats. *Gastroenterology* 1987; **93:** 550–7.

63 Dowlatshahi K, Babich D, Bangert JD, Kluiber R. Histologic evaluation of rat mammary tumor necrosis by interstitial Nd : YAG laser hyperthermia. *Lasers Surg Med* 1992; **12:** 159–64.

64 Matthewson K, Barr H, Tralau C, Bown SG. Low power interstitial Nd YAG laser photocoagulation: studies in a transplantable fibrosarcoma. *Br J Surg* 1989; **76:** 378–81.

65 Möller PH, Ivarsson K, Stenram U, Radnell M, Tranberg KG. Comparison between interstitial laser thermotherapy and excision of an adenocarcinoma transplanted into rat liver. *Br J Cancer* 1998; **77:** 1884–92.

66 Semelka RC, Ascher SM. MR imaging of the pancreas. *Radiology* 1993; **188:** 593–602.

67 Whelan WM, Wyman DR, Wilson BC. Investigations of large vessel cooling during interstitial laser heating. *Med Phys* 1995; **22:** 105–15.

68 Orth K, Russ D, Duerr J, Hibst R, Mattfeldt T, Steiner R *et al.* Laser coagulation zones induced with the Nd–YAG laser in the liver. *Lasers in Medical Science* 1997; **12:** 137–43.

69 Breedis C, Young G. The blood supply of neoplasms in the liver. *Am J Pathol* 1954; **30:** 969–85.

70 Peterson H-I. *Tumor Blood Circulation: Angiogenesis, Vascular Morphology and Blood Flow of Experimental and Human Tumors.* Miami, Florida: CRC Press, 1979.

71 Archer SG, Gray BN. Vascularization of small liver metastases. *Br J Surg* 1989; **76:** 545–8.

72 Funaki B, Rosenblum JD, Leef JA, Hackworth CA, Szymski GX, Alonso EM *et al.* Portal vein stenosis in children with segmental liver transplants: treatment with percutaneous transhepatic venoplasty. *AJR Am J Roentgenol* 1995; **165:** 161–5.

73 Waiser EM, McNees SW, DeLa Pena O *et al.* Portal venous thrombosis: percutaneous therapy and outcome. *JVIR* 1998; **9:** 119–27.

74 Steger AC, Shorvon P, Walmsley K, Chisholm R, Bown SG, Lees WR. Ultrasound features of low power interstitial laser hyperthermia. *Clin Radiol* 1992; **46:** 88–93.

75 van Hillegersberg R, de Witte MT, Kort WJ, Terpstra OT. Water-jet-cooled Nd : YAG laser coagulation of experimental liver metastases: correlation between ultrasonography and histology. *Lasers Surg Med* 1993; **13:** 332–43.

76 Amin Z, Donald JJ, Masters A, Kant R, Steger AC, Bown SG *et al.* Hepatic metastases: interstitial laser photocoagulation with real-time US monitoring and dynamic CT evaluation of treatment. *Radiology* 1993; **187:** 339–47.

77 Vogl TJ, Muller PK, Hammerstingl R, Weinhold N, Mack MG, Philipp C *et al.* Malignant liver tumors treated with MR imaging-guided laser-induced thermotherapy: technique and prospective results. *Radiology* 1995; **196:** 257–65.

78 Roberts HR, Paley M, Hall-Craggs MA, Lees WR, Friedman EP, Clemence M *et al.* Dynamic magnetic resonance control of interstitial laser photocoagulation therapy of colorectal hepatic metastases. *Lancet* 1994; **343:** 1221 (Letter).

79 Vogl TJ, Mack MG, Straub R, Roggan A, Felix R. Percutaneous MRI-guided laser-induced thermotherapy for hepatic metastases for colorectal cancer. *Lancet* 1997; **350:** 29 (Letter).

80 Lewa CJ, Majewska Z. Temperature realationships of proton-lattice relaxation time T1 in biological tissues. *Bull Cancer* 1980; **67:** 525–30.

81 Bottomley PA, Forster TH, Argersinger RE, Pfeifer LM. A review of normal tissue hydrogen NMR relaxation times and relaxation mechanisms from 1–100 Mhz: dependence on tissue type, NMR frequency, temperature, species, excision, and age. *Med Phys* 1984; **11:** 425–48.

82 Young IR, Hand JW, Oatridge A, Prior MV. Modeling and observation of temperature changes *in vivo* using MRI. *Magn Reson Med* 1994; **32:** 358–69.

83 Dickinson RJ, Hall AS, Hind AJ, Young IR. Measurement of changes in tissue temperature using MR imaging. *J Comput Assist Tomogr* 1986; **10:** 468–72.

© 1999 Blackwell Science Ltd

84 Gewiese B, Beuthan J, Fobbe F, Stiller D, Muller G, Bose Landgraf J *et al.* Magnetic resonance imaging-controlled laser-induced interstitial thermotherapy. *Invest Radiol* 1994; **29:** 345–51.
85 Stollberger R, Ascher PW, Huber D, Renhart W, Radner H, Ebner F. Temperature monitoring of interstitial thermal tissue coagulation using MR phase images. *J Magn Reson Imaging* 1998; **8:** 188–96.
86 Ishihara Y, Calderon A, Watanabe H, Okamoto K, Suzuki Y, Kuroda K *et al.* A precise and fast temperature mapping using water proton chemical shift. *Magn Reson Med* 1995; **34:** 814–23.
87 De Poorter J, de Wagter C, De Deene Y, Thomsen C, Ståhlberg F, Achten E. The proton-resonance-frequency-shift method compared with molecular diffusion for quantitative measurement of two-dimensional time-dependent temperature distribution in a phantom. *J Magn Reson* 1994; **B103:** 234–41.
88 Kuroda K, Oshio K, Chung AH, Hynynen K, Jolesz FA. Temperature mapping using the water proton chemical shift: a chemical shift selective phase mapping method. *Magn Reson Med* 1997; **38:** 845–51.
89 Sinha S, Oshiro T, Sinha U, Lufkin R. Phase imaging on a ·2-T MR scanner: application to temperature monitoring during ablation procedures. *J Magn Reson Imaging* 1997; **7:** 918–28.
90 Heisterkamp J, Matheijssen NAA, van Hillegersberg R *et al.* Accuracy of MR phase mapping for temperature monitoring during interstitial laser coagulation in liver at rest and in respiration simulation. (In press).
91 Graham SJ, Bronskill MJ, Henkelman RM. Time and temperature dependence of MR parameters during thermal coagulation of *ex vivo* rabbit muscle. *Magn Reson Med* 1998; **39:** 198–203.
92 Jolesz FA, Bleier AR, Jakab P, Ruenzel PW, Huttl K, Jako GJ. MR imaging of laser–tissue interactions. *Radiology* 1988; **168:** 249–53.
93 Morrison PR, Jolesz FA, Charous D, Mulkern RV, Hushek SG, Margolis R *et al.* MRI of laser-induced interstitial thermal injury in an *in vivo* animal liver model with histologic correlation. *J Magn Reson Imaging* 1998; **8:** 57–63.
94 Mumtaz H, Hall-Craggs MA, Wotherspoon A, Paley M, Buonaccorsi G, Amin Z *et al.* Laser therapy for breast cancer: MR imaging and histopathologic correlation. *Radiology* 1996; **200:** 651–8.
95 Roberts HR, Paley M, Sams VR *et al.* Magnetic resonance imaging control of laser destruction of hepatic metastases: correlation with post-operative dynamic helical CT. *Minimally Invasive Therapy and Allied Technologies* 1997; **6:** 41–52.
96 Hinks RS, Bronskill MJ, Kucharczyk W, Bernstein M, Collick BD, Henkelman RM. MR systems for image-guided therapy. *J Magn Reson Imaging* 1998; **8:** 19–25.
97 Gould S, Darzi A. The magnetic resonance operating theatre. *Br J Surg* 1998; **84:** 595–7.
98 Higuchi N, Bleier AR, Jolesz FA, Colucci VM, Morris JH. Magnetic resonance imaging of the acute effects of interstitial neodymium : YAG laser irradiation on tissues. *Invest Radiol* 1992; **27:** 814–21.
99 Nolsoe CP, Torp-Pedersen S, Burcharth F, Horn T, Pedersen S, Christensen NE *et al.* Interstitial hyperthermia of colorectal liver metastases with a US-guided Nd–YAG laser with a diffuser tip: a pilot clinical study. *Radiology* 1993; **187:** 333–7.
100 Schroder T, Castren-Persons M, Lehtinen A, Taavitsainen M. Percutaneous interstitial laser hyperthermia in clinical use. *Ann Chir Gynaecol* 1994; **83:** 286–90.
101 Dowlatshahi K, Saclarides T, Silver B, Fan M. Interstitial laser therapy of malignant liver tumors. *Lasers Surg Med* 1995; **18:** 18 (Abstract).
102 Tranberg KG, Moller PH, Hannesson P, Stenram U. Interstitial laser treatment of malignant tumours: initial experience. *Eur J Surg Oncol* 1996; **22:** 47–54.
103 Gillams AR, Brookes J, Hare C *et al.* Follow up of patients with metastatic liver lesions treated with interstitial laser therapy. *Br J Cancer* 1997; **76:** 31 (Abstract).
104 Hashimoto D, Takami M, Idezuki Y. In depth radiation therapy by YAG laser for malignant tumors of the liver under ultrasound imaging. *Gastroenterology* 1985; **88:** 1663 (Abstract).
105 Hahl J, Haapiainen R, Ovaska J, Puolakkainen P, Schroder T. Laser-induced hyperthermia in the treatment of liver tumors. *Lasers Surg Med* 1990; **10:** 319–21.
106 Huang GT, Wang TH, Sheu JC, Daikuzono N, Sung JL, Wu MZ *et al.* Low-power laserthermia for the treatment of small hepatocellular carcinoma. *Eur J Cancer* 1991; **27:** 1622–7.
107 Steger AC, Lees WR, Walmsley K, Bown SG. Interstitial laser hyperthermia: a new approach to local destruction of tumours. *BMJ* 1989; **299:** 362–5.
108 Lee FT Jr, Mahvi DM, Chosy SG, Onik GM, Wong WS, Littrup PJ *et al.* Hepatic cryosurgery with intraoperative US guidance. *Radiology* 1997; **202:** 624–32.
109 Vogl TJ, Mack MG, Muller P, Straub R, Eichler K, Felix R. Laser-induced and microwave thermotherapy of hepatocellular carcinoma. *Digestion* 1998; **59**(Suppl 2)**:** 86–8.
110 Goto Y, Nagino M, Nimura Y. Doppler estimation of portal blood flow after percutaneous transhepatic portal vein embolization. *Ann Surg* 1998; **228:** 209–13.
111 Klotz HP, Flury R, Erhart P, Steiner P, Debatin JF, Uhlschmid G *et al.* Magnetic resonance-guided laparoscopic interstitial laser therapy of the liver. *Am J Surg* 1997; **174:** 448–51.
112 Cuschieri A, Crosthwaite G, Shimi S, Pietrabissa A, Joypaul V, Tair I *et al.* Hepatic cryotherapy for liver tumors. Development and clinical evaluation of a high-efficiency insulated multineedle probe system for open and laparoscopic use. *Surg Endosc* 1995; **9:** 483–9.

 © 1999 Blackwell Science Ltd