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Low-power Laserthermia for the Treatment of Small Hepatocellular Carcinoma

Guan-Tarn Huang, Teh-Hong Wang, Jin-Chuan Sheu, Norio Daikuzono, Juei-Low Sung, Mu-Zong Wu and Ding-Shinn Chen

Laserthermia by a novel interstitial probe adapted to low power Nd-YAG laser machine was used to treat small hepatocellular carcinoma (HCC). The set condition was 43–45°C in thermocouple with power of 2–3 W and the duration 20–30 min. In the 5 cases studied, 1 had a good result with total necrosis of the tumour without recurrence in 16 months. 1 died of liver failure 2.5 months later although death was not related to the procedure. 1 patient died of progressive disease 18 months later. The remaining 2 had recurrent tumours 5 and 12 months later, although the treated small tumours showed good response. Histological examination showed cell degeneration and necrosis. It is concluded that laserthermia is potentially useful in the treatment of the patients with small HCC.
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INTRODUCTION

HEPATOCELLULAR CARCINOMA (HCC) is one of the most prevalent malignancies in the orient and sub-Saharan Africa, and the prognosis is poor [1]. With the development of new diagnostic modalities, early detection is now possible [2] and the clinicopathological features are now clearer [3]. For the treatment of HCC, surgical resection is the first choice [4]. For inoperable HCC, transcatheter hepatic arterial embolisation (TAE) has been shown to improve prognosis [4]. However, these treatments are not always satisfactory, and the results of chemotherapy are very poor [5]. Novel modalities of treatments, such as intratumour injection of absolute ethanol [6, 7], OK-432 [8], or interleukin 2 and lymphokine-activated killer cells [9] have also been developed. Although beneficial, there are still drawbacks in these treatments.

Laser therapy has been employed in the treatment of cancer, and laser vaporisation has been used to treat HCC [10]. Laserthermia for metastatic hepatic tumours with frosted laser scalpels has also been reported [11]. However, all of these techniques need laparotomy, and are applicable only to tumours located superficially. For a deeply seated HCC, laser vaporisation or high-power laserthermia with a scalpel is not feasible because of the generation of much heat and gas. By contrast, laserthermia with an interstitial probe and low-power lasers under computer control and thermocouple monitoring does not have such shortcomings [12] and will probably be useful in the treatment of HCC. In recent years, thermal necrosis due to intrahepatic Nd-YAG laser photocoagulation in rats [13] and interstitial laser hyperthermia in the normal canine liver [14] have been studied. Treatment of metastatic cancer of the liver with bare fibres and Nd-YAG lasers under ultrasound guidance has also been reported, with satisfactory results [15]. However, monitoring the temperature in this system is difficult. In the present study, we tried laserthermia in treating small HCC via percutaneous puncture under ultrasound guidance with a newly designed interstitial probe—a hybrid probe which has good laser diffusion and a well controlled temperature monitor. The preliminary results are reported here.

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MATERIALS AND METHODS

Design of the hybrid probe

The newly designed interstitial probe is mainly composed of four parts: the flexible 400 micron quartz fiber for laser conduction, with fibre core 1 cm in length for laser irradiation, laser diffusing material around the fibre core to improve laser diffusion, and a laser transmissive mechanical support tube to

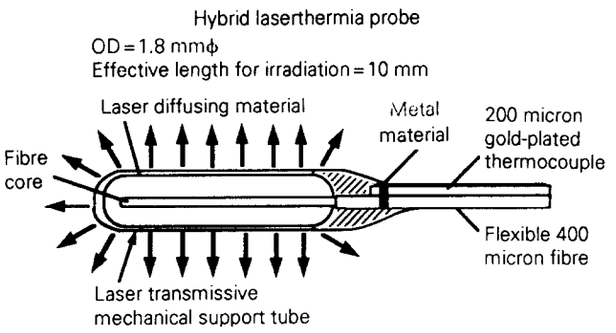


Fig. 1. The hybrid probe designed for laserthermia.

protect the fibre core and support the laser diffusing material (Fig. 1). A 200 micron gold-plated thermocouple was set slightly backward to the fibre core to act as a temperature guide for subsequent laser power setting. A small metal substance was coated around the probe just behind the tip of thermocouple to make it visible ultrasonically. The laser machine used was a Nd-YAG laser system (SLT contact laser system model CL 50, Surgical Laser Technologies, Tokyo, Japan) combined with an SLT laserthermia feedback system (Surgical Laser Technologies).

Animal experiments to evaluate the temperature map

Before animal study, extensive testings of the probe were performed in pig livers. The temperature map to test the even thermal distribution with variable temperature setting in thermocouple was established. Multiple sessions of hyperthermia were done *in vitro* in pig livers to test the stability of the probe, and unsatisfactory products were discarded. Further tests were done *in vivo* in rabbits for temperature map and safety. The rabbits (New Zealand White, about 4 kg in weight) were anaesthetised with ketamine (10 mg/kg intramuscular injection) for the hyperthermia study and then put on supine position. After laparotomy, the hybrid probe was inserted into the liver directly, low-power laser was applied to achieve the temperature of thermocouple at 43–45°C, and the temperature was measured at different distance from the hybrid probe with another thermocouple system. At the same time, percutaneous puncture into the liver under direct observation (imitating the puncture procedure in humans) was also tested, to check the flexibility of the probe and the possibility of bleeding or liver injury. All the rabbits received good care.

In the animal experiments, when the guided temperature of the thermocouple was set at 44–45°C, power of 2–3 W was the most suitable for each probe to maintain a stable temperature curve in the set range. The temperature near the centre of probe was between 55–60°C, and could be obtained immediately. The area where the temperature was constantly over 42°C was about 3 cm in diameter around the probe. During laserthermia, the temperature just near the probe increased gradually, and the temperature did not reach 80°C. Suboptimal power will generate a temperature at the lower range or even below that needed, and higher power will sometimes create transient high temperatures which might damage the probe, although the laser power would be cut automatically. After several 10-min sessions of laserthermia, rabbits were killed. The livers were removed and sectioned serially to check the coagulation area due to laser heat. If the temperature of thermocouple was set at 42°C, the effective area (>42°C) for laserthermia was about 2 cm in diameter.

Laserthermia for human small HCC

After detection of small hepatic tumours by ultrasound, the patients were studied with computed tomography (CT). Angiography was also done if there was no contraindication. The coagulation profile was checked, with criteria of platelets $\geq 5 \times 10^4/mm^3$, prothrombin time $\leq$5s prolongation, and the bleeding time $\leq$5 min. HCC was confirmed histologically with ultrasound-guided biopsies. Laserthermia was applied only if the patient was not a candidate for surgery or TAE. Before laserthermia, the patient and family were informed of the procedures and the experimental nature of this study. Informed consent was obtained from every patient.

In total, 5 cases (4 men and 1 woman) of small HCC were studied (Table 1). All 5 were asymptomatic and the tumours were detected during regular follow-up ultrasound examination because of chronic liver disease [2]. All tumours were smaller than 5 cm, and all patients had cirrhosis, with Child classification A in 2, B in 2 and C in 1. 2 had the HCC in the left lobe, 2 in anterior middle portion of the right lobe with locations easily approached by linear puncture probes, and 1 had a HCC in the posterior portion of the right lobe, where the sector probe with puncture adaptor was the suitable approach. The reasons of laserthermia trial for each patient were as follows: severe atherosclerosis made TAE impossible for case 1 who had multiple tumours, cases 2 and 3 had poor renal function, and thus angiography and operation were regarded as risky, and poor liver reserve precluded TAE or surgery for case 4. Only case 5 was suitable for surgical resection of the tumour or TAE, but the patient and her family refused either treatment and agreed to try laserthermia.

The conditions for laserthermia in patients were deduced from the animal experiments. Power of 2–3 W was used to achieve the temperature 43–45°C at the thermocouple for a tumour 2–3 cm in size, and the duration of laserthermia was maintained for 20–30 min. For the patient's safety and satisfactory results, a probe usually was not used for more than 5 sessions, because its fibre core was sometimes broken after multiple use.

The procedures of laserthermia were as follows. A 16G Medicut cannula (Sherwood Medical, St Louis, Missouri) was inserted into the centre of the tumour under ultrasound guidance (SSD-630) and a 3.5 MHz linear puncture probe or a 3.5 MHz sector probe with puncture adaptor (Aloka, Tokyo). The inner metal needle was pulled out and the polypropylene cannula retained in position. The hybrid probe was then inserted into the centre of the tumour through the polypropylene cannula. Laserthermia then commenced. During laserthermia, no gas or fluid flow was used for cooling.

Before and after the procedures, no prophylactic antibiotics was given. The patients were followed with ultrasound every 3–7 days, and CT about 2 weeks later. Ultrasound-guided biopsy of the hepatic tumour was also performed 1–2 weeks after laserthermia. Usually, the histological findings of the HCC helped to determine the necessity of subsequent sessions of laserthermia. If the tumour cells showed degeneration or necrosis in multiple biopsy specimens, the treatment was then regarded successful. Imaging studies for possible effects of laserthermia were repeatedly re-evaluated.

RESULTS

Animal experiments

In pig liver testings, the temperature was evenly distributed without focal high temperature. No carbonisation or vaporis-

Table 1. *5 cases receiving laserthermia treatment for small hepatocellular carcinoma*

Case (age, sex)	Child's classification	Pathology	Tumour size (cm)	Reasons for laserthermia	Outcome	Histological findings after treatment	AFP level (ng/ml)*
1 (63, M)	A	LC + HCC	4.2 × 4.2 2.0 × 2.0 2.0 × 2.0	TAE failed	New tumour 5 mo later, died 18 mo	Degeneration, coagulation	38/67
2 (79, M)	B	LC + HCC	1.6 × 1.7	Azotemia	Recurrence 5 mo later	Degeneration, necrosis	117/172
3 (60, M)	B	LC + HCC	2.4 × 2.2	Azotemia	Good	Degeneration	<20/<20
4 (48, M)	C	LC + HCC	2.8 × 2.2	Poor liver reserve	Died of liver failure	(Not done)	<20/<20
5 (61, F)	A	LC + HCC	2.1 × 1.9	Refuse surgery and TAE	Recurrence 12 mo later, retreated	Necrosis	366/<20

AFP = alpha-fetoprotein, LC = liver cirrhosis, HCC = hepatocellular carcinoma.
*Pre/post-treatment. Normal range <20 ng/ml.
There was no change in liver function after treatment in any patient.

ation was noted. The probes usually remained functioning after multiple uses. In the *in vivo* studies in rabbits, after percutaneous puncture into the liver, the probe moved with the respiratory movements of the liver. Only mild oozing from the puncture hole was seen after laserthermia for 10 min and removal of the needle. It was easy to stop the bleeding by compressing with the fingers for several minutes. The rabbit was further observed for another 10–20 min, and no bleeding was ever noted. There was no gross liver laceration. An area about 1 cm in diameter due to direct heat coagulation was found, but no carbonisation or evidence of vaporisation was seen (Fig. 2).

Case study

Side-effects. All patients tolerated the procedures of laserthermia well. And there were no side-effects except in case 4, who complained of mild right upper quadrant pain after laserthermia.

Image findings. In patients, immediately after laserthermia, a hyperechoic area within the tumour appeared on ultrasound examination (Fig 3a, b). Usually, a hyperechoic line was seen along the puncture route after laserthermia. The hyperechogenicity within the tumour disappeared within 3 days, but the hyperechoic line along the puncture route persisted for a longer time, sometimes even lasting for several months. Later on, the echodensity of the tumour decreased to hypoechoic picture with anechoic portion (Fig. 3c) or even disappearance of tumour echo with development of the effects of laserthermia. In CT, a larger, more hypodense area representing extensive necrosis of the tumour and the adjacent liver tissues was seen, and later the tumour became more hypodense with decreased tumour size (Fig. 4).

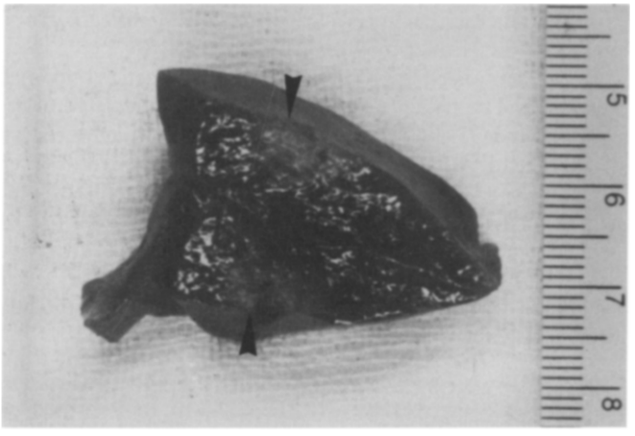


Fig. 2. Liver specimen of a rabbit 10 min after laserthermia showing focal coagulation (arrowheads).

Histological findings. Degeneration and necrosis of tumour cells were the main histological changes 3–40 days after laserthermia in the 5 tumours of less than 3 cm from 4 cases who received follow-up biopsies. In the larger tumour (4.2 cm in diameter) of case 1, there were still viable tumour cells in the tumour periphery. Microscopically, at the area near the laser probe, direct tissue coagulation (Fig. 5a) and thickening of vessel wall were seen, and in the area effective for laserthermia, cell degeneration was prominent. As shown in Figs 5b, c, disarrangement, swelling and even vacuolisation of cells were noted. The nuclear margin became irregular, and some cell necrosis was also seen. Two tumour specimens were studied by electron microscopy (EM) after 30 min of laserthermia, the main findings being in the cytoplasm: the shape of the mitochondria became irregular and the endoplasmic reticulum swelled, the organelles in the cytoplasm decreased and some degeneration pigment was present within the cytoplasm (Fig. 6). The cell was swollen and the cytoplasmic membranes were damaged.

Follow-up results. In the 5 cases treated by laserthermia, 1 (case 4) died of chronic liver failure 2.5 months after laserthermia. However, this was not related to the treatment, since the patient already had poor liver function before the trial. Follow-up biopsy of the tumour was not done, and the detail of the treated HCC was not known. 1 (case 1) had multiple recurrent tumours 5 months later and died of progressive disease 18 months later. 1 (case 3) had good results with complete necrosis of the tumour in image studies and was free of recurrence in a follow-up period of 16 months. The remaining 2 had recurrent tumours at different sites of the liver 5 (case 2) and 12 months (case 5) later, although the treated small tumours had good responses and the patients are alive at the time of writing. Case 5 received laserthermia again after recurrence, and results were again successful. Serum alpha-fetoprotein (AFP) level decreased from 366 ng/ml to normal for case 5 after treatment. Another 2

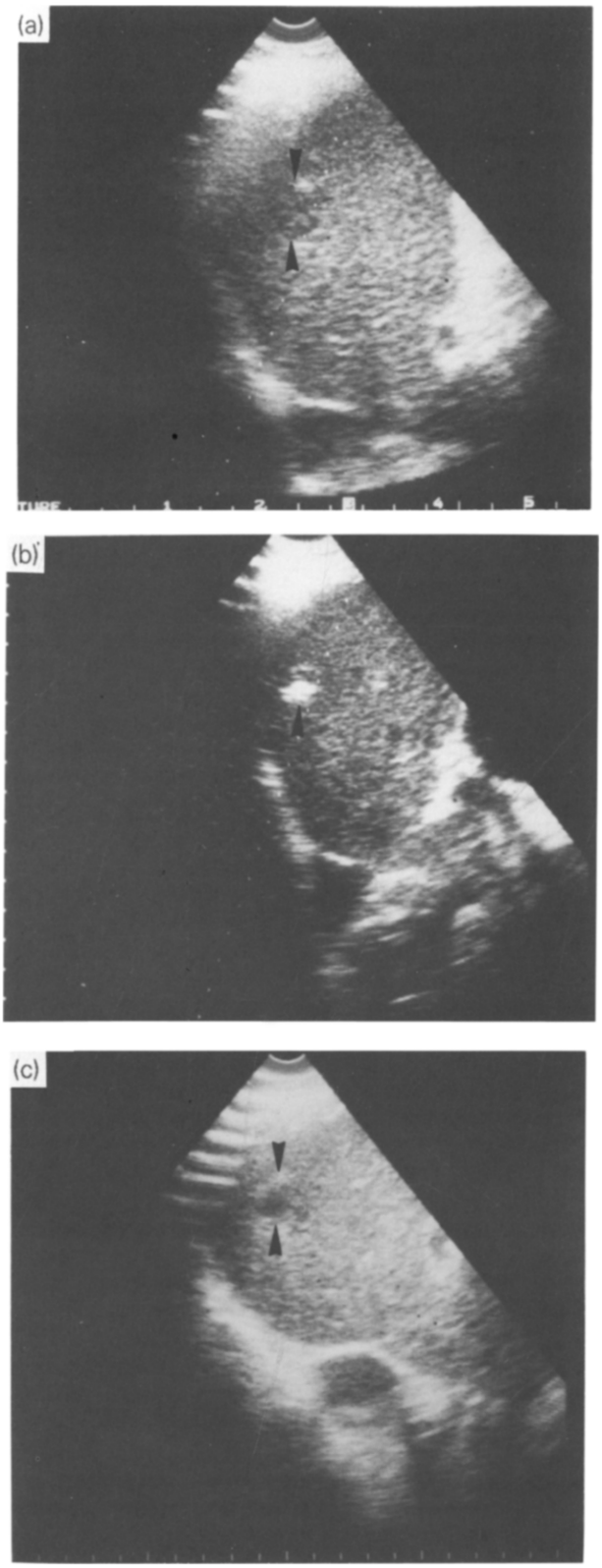


Fig. 3. The sonographic pictures before and after laserthermia of case 3. (a) A small hypoechoic tumour was detected by ultrasound (arrowheads). (b) Immediately after laserthermia, a hyperechoic area was seen (arrowheads). (c) 4 months later, the tumour was more hypoechoic, and partly anechoic (arrowheads).

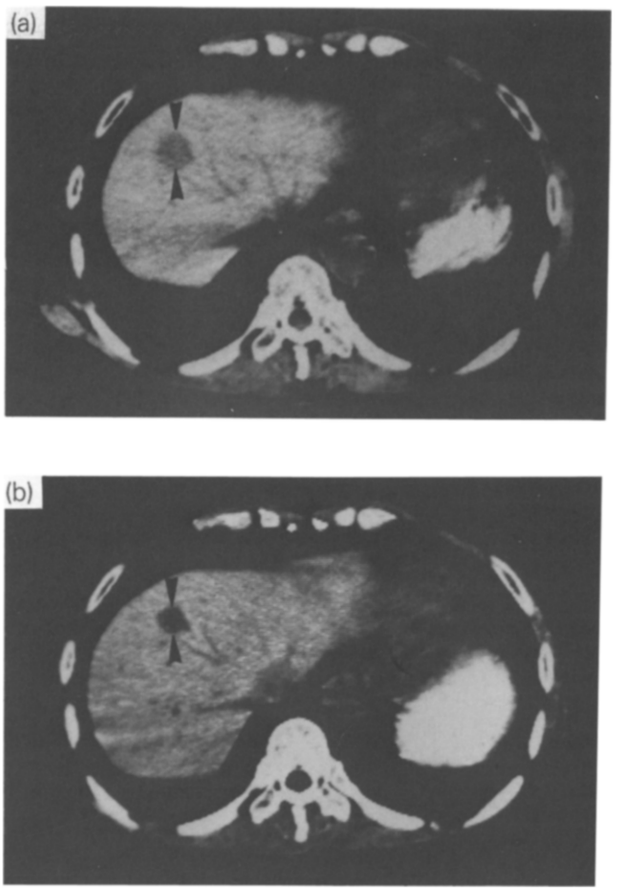


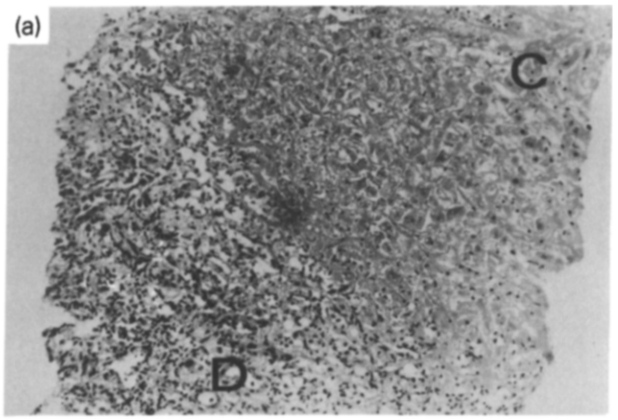
Fig. 4. CT scan before and after laserthermia in case 3. (a) A small hypodense tumour and (b) A more hypodense and cystic area with decreased tumour size in the same plane, 5 months after laserthermia.

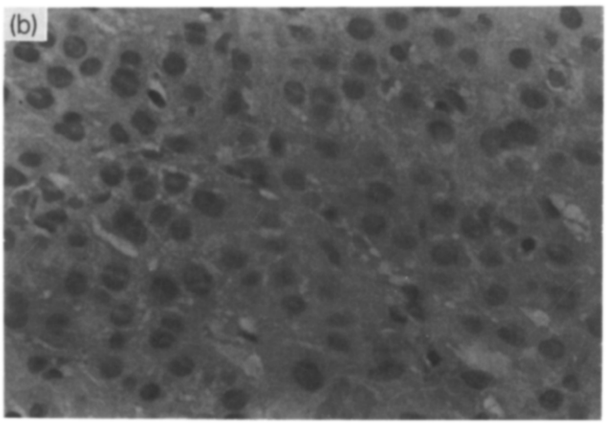
showed slightly increased AFP value than that before treatment. Follow-up liver and renal function tests were stable and the patients remained asymptomatic despite the existing liver cirrhosis and/or azotaemia in the 3 surviving patients.

DISCUSSION

For the treatment of small HCC, surgical resection and TAE are well established procedures [4]. For HCC patients with inadequate liver reserve, however, these treatments are frequently impossible or even contraindicated, and accordingly, new methods of treatment are necessary. Among them, direct intratumour therapy with absolute ethanol has been shown to be helpful [6, 7, 16]. However, intratumour injection of absolute ethanol may sometimes induce deteriorated liver function [6], this local treatment should therefore be regarded risky when the liver reserves are poor. Treatments with direct physical effects such as hyperthermia [17] or with other medication not damaging the nontumourous liver, such as OK-432[8] or interleukin-2 and lymphokine-activated killer cells [9] have also been reported. The newly developed laserthermia procedure with lower-power lasers and interstitial probes, as described in this report, adds to the list of potentially useful modes of treatment for HCC.

Since percutaneous puncture to approach the hepatic tumour under ultrasound guidance is well-established, the hybrid probe can be put at a proper position for laserthermia [15]. Because the probe is flexible, it can be retained within the tumour for 30 min after insertion without injury to the liver, and the patient can breathe normally. Although air emboli have been reported





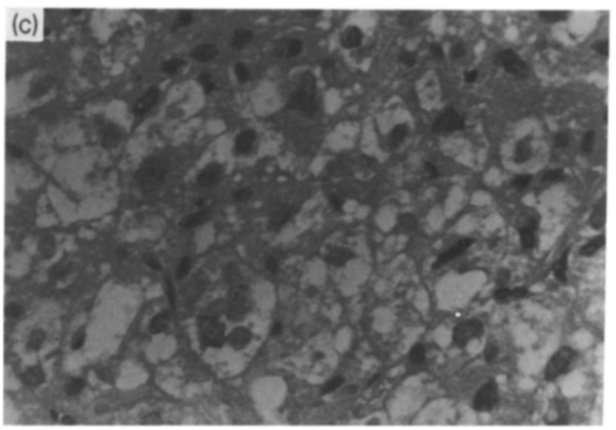


Fig. 5. The histological findings of HCC specimens after laserthermia. (a) An area of direct coagulation necrosis (C) and an area of cell degeneration (D) and were seen 3 days after laserthermia (100 ×, H and E stain). (b) HCC tissue before treatment (400 ×, H and E stain). (c) Cell swelling, degeneration, vacuolisation and irregular nuclear margin were present 20 days after laserthermia (400 ×, H and E stain).

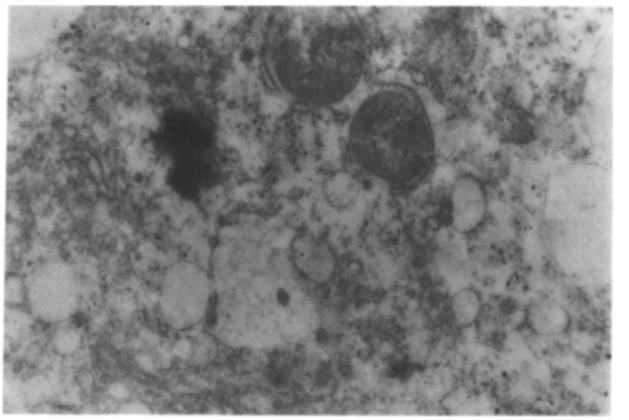


Fig. 6. Electron micrograph of HCC cell after laserthermia for 30 min (specimen taken 40 days after laserthermia) showing damaged mitochondria and decreased organelles within the cytoplasm (12 000 ×).

after hyperthermia for tumour metastasis within the liver [11], the risk was eliminated in our study as no gas or fluid flow was used in our system. Compared with a previous study which showed tumour necrosis by Nd-YAG transmitted with multiple bare fibres [15], we used the rather lower temperature range and treated an extended area (up to 3 cm). This was possible due to improved characteristics of the special design in our system. The diffusing material makes the laser heat diffuse well, without keeping the heat localised near the tip. The effect to the tumour cells is degeneration rather than thermal necrosis, and because of the strict temperature monitor, complications due to high temperature are not likely to occur.

Although results of animal experiments cannot be applied completely to humans, they yield invaluable information. Therefore, a temperature map measured in normal rabbit livers was necessary before human study, and served as a guide to intrahepatic laserthermia. From our animal experiments, we anticipated that the effective area of laserthermia was about 3 cm in the conditions set up here. However, there are many factors which would influence the effective area of the hybrid probe. The difference in vasculatures between normal liver and HCC, or between human and rabbit livers probably influences the effective area, and the liver size may also affect the distribution of the heat. Additionally, laparotomy during an animal study is different from the condition of direct percutaneous puncture in humans. Besides the effects of hyperthermia, direct effects of the laser to HCC and the normal liver might also differ. Further animal and human studies are necessary to define and resolve these questions.

From the imaging studies and follow-up biopsies, laserthermia was shown to have tumourcidal effects. This new therapeutic approach may be helpful to patients with small HCC with poor liver reserve. Like TAE or other percutaneous intratumour therapies, it is at least a palliative treatment for small HCC. Compared with the other direct intratumour therapy such as pure ethanol [6] or OK-432 [8] performed in our institute, laserthermia seems to cover the whole tumour better because of the highly effective temperature distribution. In our hands, laserthermia also has the advantage of less treatment sessions; usually once or twice will suffice. With optimisation of power, duration and therapeutic sessions, laserthermia may have the potentiality of becoming a modality of non-surgical curable treatment.

Because no major side-effects were noted in our preliminary study, it seems feasible to study this new treatment modality in more patients. Meantime, an improved probe to cover a larger area for laserthermia is to be designed and used. In addition, laserthermia combined with photodynamic therapy, or combined with TAE should also be evaluated to try to cure small HCC. Finally, the definite effects of this novel anticancer

treatment for HCC should be concluded only after prolonged follow-up studies are completed in more patients.

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Mitoxantrone in Malignant Pleural Mesothelioma: A Study by the EORTC Lung Cancer Cooperative Group

Frans J.M. van Breukelen, Karin Mattson, Giuseppe Giaccone, Nico van Zandwijk, Hans T. Planteydt, Anne Kirkpatrick and Otilia Dalesio

46 patients with malignant pleural mesothelioma were entered in a phase II study of mitoxantrone 14 mg/m² every 3 weeks. Histology was confirmed by a pathology panel. None of the patients had received previous chemotherapy. Toxicity was mainly mild gastrointestinal and haematological side-effects. Out of 34 patients evaluated for response, only 1 partial response was recorded. Mitoxantrone at this dose and schedule has marginal activity in malignant mesothelioma.
Eur J Cancer, Vol. 27, No. 12, pp. 1627–1629, 1991.

INTRODUCTION

CHEMOTHERAPY OF malignant mesothelioma is disappointing. Doxorubicin has been reported to be one of the most active agents, with a cumulative response rate of 18% in 164 evaluable patients [1]. Combinations including doxorubicin or other drugs do not significantly improve response rates over doxorubicin alone [1]. Mitoxantrone is a synthetic anthracenedione [2]; its antitumour activity is related to DNA intercalation [3] and topoisomerase II inhibition [4]. Mitoxantrone is less cardiotoxic than doxorubicin [5, 6] and is an active drug in breast cancer and leukaemia [2, 7]. The EORTC Lung Cancer Cooperative Group has completed a phase II of mitoxantrone in malignant mesothelioma.

PATIENTS AND METHODS

To be eligible, patients had to have histologically confirmed diagnosis of malignant mesothelioma with measurable or evaluable lesions, Karnofsky performance status 60% or higher, no other malignancies, normal bone marrow reserve, normal liver, kidney and cardiac functions and be aged 75 or under. Previous chemotherapy, radiotherapy or intracavitary therapy with anticancer drugs were exclusion criteria. Informed consent was obtained in all patients. Pathology was reassessed by a central pathology panel and diagnosis of mesothelioma was classified as definite, probable, possible, improbable, or excluded. Only cases classified as definite or probable were considered eligible for this study.