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Interstitial Laser Thermotherapy in Neurosurgery: A Review

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Summary

One of the most recent laser treatment modalities in neurosurgery is interstitial laser thermotherapy (ILTT). In this review, experimental and clinical studies concerning intracranial ILTT are discussed. Two methods for intra-operative control of the laser induced lesions are described; i.e., computer-controlled power delivery, using a thermocouple that is positioned interstitially at the periphery of the tumour to maintain the desired temperature at that point, and MRI, to visualise the extent of the thermal lesions induced by ILTT. The results show that ILTT using a Nd:YAG laser is easy and relatively effective in the treatment of small deep-seated brain tumours with minimal risk and complications. This review is concluded with suggestions for further improvement of this treatment modality.

Keywords: Brain tumours; laser surgery; MRI; photocoagulation; stereotaxy; ultrasound.

Introduction

The use of laser treatment of brain tumours is now well documented. These therapeutic modalities include photovaporisation [44], non-contact photocoagulation [29], and photodynamic therapy (PDT) [21]. In 1990, Sugiyama *et al.* [39] were the first to report on interstitial laser thermotherapy (ILTT) of brain tumours. ILTT is based on interstitial tissue destruction by means of laser coagulation as well as hyperthermia and was described first by Bown in 1983 [7]. Since then several experimental and clinical studies in liver [37], pancreas [14], prostate [40], head and neck [26] and brain have been performed [31, 39]. The purpose of this article is to present the current status of ILTT for the treatment of intracranial tumours, to discuss its possibilities in neurosurgery, and to suggest possible improvements.

Basic Principle of ILTT

In ILTT of brain tumours, laser light is interstitially delivered by a stereotactical procedure into tumours through one or more optical fibres. The laser light is deposited at low powers (1–5 W) and long exposure times (3–45 min), resulting in an increase in temperature in the target area. The basic principle of ILTT is the absorption of light and its conversion into heat. The tissue response depends on the temperature distribution as a function of time. The temperature distribution is dependent on the light distribution, the tissue absorption, and the heat transfer in the tissue. The light distribution is determined by the optical properties of tissue, i.e., by the tissue scattering and absorption. The optical properties determine the optical penetration depth (the depth at which the intensity of light drops to e^{-1}, or $\approx 37\%$, of its original value). In the adult brain the optical penetration depth is maximal (3–5 mm) in the near-infrared part of the electromagnetic spectrum [9, 42]. In tumours, like malignant glioma, the optical penetration depth of red and near-infrared light ($\lambda = 600$ to 1200 nm) is about three times larger than that in the normal brain [43]. The light distribution is also determined by the properties of the fibre and fibre tip that is used like its shape and index of refraction. Several fibre tips have been used, such as a bare fibre [33], a frosted fibre tip [39], a cylindrical diffuser tip [31], and a quartz tip [1, 20]. Thus, the light distribution or fluence rate in the tissue is determined by the optical properties of tissue (dependent on wavelength), by the laser power, and by the fibre tip geometry. As in ILTT the fibre tip is in contact with the tissue, the index of refraction of the

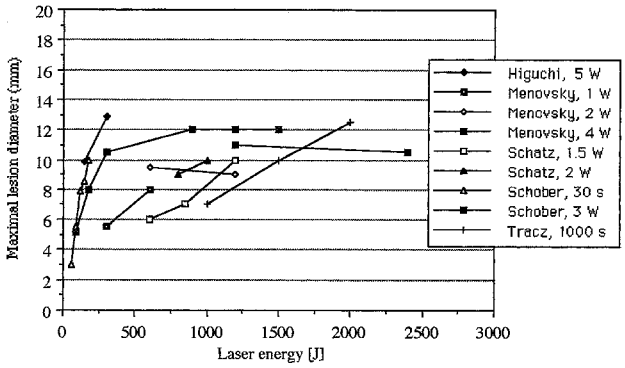

Fig. 1. Maximal lesion diameter of the thermal damage vs. laser energy-power [*W*] x time [*s*] = energy [*J*]- as found in the experimental studies by Higuchi [18], Menovsky [25], Schatz [33], Schober [34], and Tracz [46]

tissue and the quality of the contact between the tip and the tissue affect the light distribution and therefore the thermal distribution of laser energy. The light is converted into heat by absorption in the tissue. The local heat production in the tissue is determined by the product of the (local) light fluence rate and the (local) tissue absorption. Absorption in the near-infrared is primarily due to the presence of chromophores such as haemoglobin and water. The Neodymium:Yttrium-Aluminium-Garnet (Nd:YAG) laser at 1064 nm has gained favour for ILTT because of its deep penetration in combination with a relatively high blood absorption [9, 41]. As a result, the Nd:YAG laser has excellent coagulative properties. After absorption in the tissue chromophores, the heat is conducted to the surrounding tissue. Heat transfer in tissue is primarily dependent on conduction and convection by blood flow.

In ILTT, the temperature is maximal around the fibre and declines gradually to the periphery. At temperatures exceeding 100 °C, vaporisation of water and tissue carbonisation occurs [45]. Water vaporisation results in steam development, undesired pressure effects, and cavity formation. For ILTT, the temperature range of 45–90 °C is optimal. These temperatures cause an irreversible tissue coagulation of healthy and malignant tissue [45], in the normal brain characterised by a generally preserved tissue structure with dilatation of capillaries, and various changes in nuclei, membranes, and cytoplasm [34]. Temperatures between 42.5 and 45.5 °C may show a small degree of selectivity for destruction of malignant cells called hyperthermia [17]. This possible thermosensibility is probably the result of a poor vascular system in the tumour and an altered cellular microenvironment of the tumour cells. Because of the often insufficient vascularisation of the tumour, heat convection by the blood vessels is minimal and causes a higher temperature in the tumour [12]. Moreover, inadequate vascularisation results in changes of the microenvironment of the tumour cells, such as a low pH, hypoxia, and nutrients deficiency, factors which enhance the hyperthermic cell killing [15, 16]. Furthermore, the microvasculature of tumours is damaged more easily by heat than normal microvasculature [10, 27].

Experimental Studies

Animal experiments on ILTT concern dose-response and histology in normal brain, ILTT in a brain tumour model, and monitoring of laser-tissue interaction by MRI. All these ILTT studies were performed with the Nd:YAG laser using various fibre tips.

Dose-Response

The size of the thermal lesion in brain is dependent on the laser parameters and the size and shape of the fibre tip that is used. In the dose-response studies, the size of the thermal lesion represents the coagulation zone, both macroscopically and microscopically visible. In the studies included in this review, no distinction was made between the damage produced by coagulation and that produced by temperatures in the hyperthermia range. In general, the size of the lesions increased with both the total energy and the power delivered [18, 25, 33, 34, 46]. Figure 1 shows the relation between the maximum lesion diameter and the energy according to experimental studies in normal brain in various animals. It has been shown that irradiation at relatively high irradiances (power > 3 W with a damage fibre tip) resulted in herniation and/or displacement of the brain and subsequent death of the animals [33].

Histology Following ILTT

The early and late histological changes in the brain following interstitial laser irradiation were studied in rats [34], rabbits [18, 33], cats [46], and pigs [25]. In general, the acute laser-induced lesions show a distinct morphological architecture, consisting of 3 to 4 relatively sharply demarcated zones.

When high irradiances are used with temperatures higher than 100 ° C, a haemorrhagic pseudo cavity is created in the immediate vincity of the fibre tip [18, 25, 33, 46]. This cavity contains some fibrin and debris with charred and carbonised tissue at the margins [25, 46]. With temperatures lower than 100 ° C, the central lesion consists of densely coagulated tissue, in which the neurons, glial cells, and vessels are destroyed [46]. However, the overall tissue structure is well distinguishable. Ultrastructural study reveals generalised damage of cellular and subcellular membranes [34]. The next zone has almost the same features as the densely coagulated tissue, except that this zone is dispersed due to the infiltration of interstitial fluid. Finally, the outer zone is marked by oedema and consists of viable brain which is sharply demarcated from the zone of dispersed coagulation tissue [25]. Some neuronal shrinkage, axonal swelling, and hypertrophic nuclei of endothelial cells of vessels is present [18, 46]. No evidence of thrombosis and/or mem-

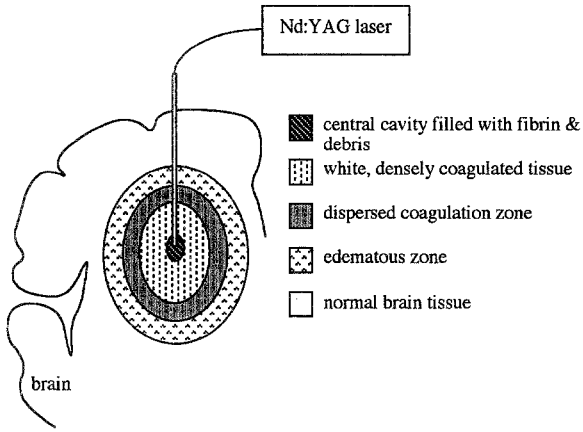

Fig. 2. A schematic drawing of the different zones of histology of the thermal lesion following interstitial laser irradiation

brane disruptions is seen in this zone [34]. This oedematous zone is sharply demarcated from the normal brain tissue [34, 46]. Tracz *et al.* defined the central core and the subsequent densely coagulated zone as the inner lesion, while the inner lesion together with the dispersed coagulation zone and the oedematous zone was defined as the outer or total lesion [46, 47]. Figure 2 gives a schematic view of the different histological zones of the thermal lesion.

In the first 48 hours following ILTT, the total lesion size increases with a factor of 1.2 to 1.5 and is maximal at 48 hours after irradiation [34, 46, 47]. This phenomena is attributed to additional hyperthermic cell death at the periphery of the lesion, and due to perifocal oedema and/or disturbance of the perilesional microcirculation [33, 47]. In the first week after irradiation, the central zone of coagulation becomes necrotic and a resorptive reaction starts from the periphery, consisting of neutropil infiltration, in-growth and proliferation of capillaries, transformation of macrophages to gitter cells, and infiltration by microglial cells [33, 34]. At the periphery of the lesion, the oedema spreads into adjacent normal tissue [34]. At 1 week, granulation tissue surrounding the necrotic zone is present, slowly proceeding towards the centre of the lesion. From day 0 till day 14 the lesion shrinks in the first 14 days with 50% [47]. In the following weeks, the centre of the necrosis becomes a cystic defect ensheathed by a thin fibrous capsule with gitter cells and a few siderophages and lymphocytes [34]. Glial scarring and demyelination is minimal and the blood-brain barrier is broken at the site of the lesion. It remains open up to 6 days after irradiation.

ILTT in Brain Tumour Model

At this moment, there is only one well documented report on ILTT in a brain tumour model. El-Ouahabi *et al.* used MRI to guide and monitor ILTT in a C6 rat tumour model [11]. Fourteen or 21 days after implantation of the tumour ILTT was performed at 3.2 W for 30 or 60 s. The results showed that laser irradiated rats had no significant increase in mean survival compared to the tumour bearing control rats that were not treated.

Monitoring of Laser-Tissue Interaction

In interstitial laser therapy there is no direct visual control of the treated volume. Therefore, ILTT requires real-time imaging modalities to control and monitor treatment. Laser-tissue intiractions can be noninvasively monitored by ultrasonography (US), computed tomography (CT), and MRI [19]. Because of artefacts from the skull, ultrasonographic monitoring is not feasible in intracranial procedures with an intact cranium. CT scan is limited in the real-time monitoring of intracranial laser-tissue interaction, as this technique has low soft-tissue contrast resolution and its sensitivity to early tissue changes following laser irradiation is poor. Moreover, the images obtained are restricted to the coronal plane. In contrast, MRI has been shown to have more potential to visualise and monitor laser-tissue interactions [19]. It has an excellent soft-tissue contrast resolution and images section can be obtained in any direction. The basis for MRI monitoring of laser-tissue interactions are the structural alterations of macromolecules in the tissue. Following laser irradiation, the amount, the distribution, and the mobility of water and lipid molecules are altered, parameters to which the MR signal is sensitive [6]. MR signals are also temperature sensitive, raising the possibility of real-time imaging of ILTT with MRI. Moreover, metabolic, physicochemical, and perfusion changes which occur after laser irradiation will also influence the MR signal.

The possibility of MR imaging of laser-tissue interactions in brain was firstly investigated by Jolesz *et al.* [19]. During laser irradiation in vitro in the rabbit brain, there was a complete loss of signal intensity at the fibre tip, and a decreased signal intensity in the periphery of the lesion. After irradiation, the peripheral signal contribution returned to its normal intensity. Furthermore, it was shown that MRI can be used to determine the position of the fibre tip and to distinguish between reversible and irreversible changes in the tissue. The authors suggested that the complete signal loss was a combination of tissue water loss and altered tissue water mobility, while the reversible signal loss was the effect of a rise in temperature itself. In an in vivo study, a correlation was found between the MR signal and histological changes in the tissue [19]. The optical fibre was seen as a dark line, while the central cavitation was seen as a signal loss on all images. The coagulation zone was represented by an increased T1w (T1 weighted image) signal, and a decreased T2w signal. On T2w images, a bright ring at the periphery of the lesion represented histologically confirmed brain oedema.

Tracz *et al.* performed a study of MR imaging of laser irradiation in cat brains [46, 47]. In almost all cases, T2w images of the lesions acquired during irradiation consisted of a dark-to-hypointense region. In some cases, this central region was bright. T2w images acquired immediately and at 48 hours after laser irradiation consisted of a dark-to-isointense region circumscribed by a hyperintense-to-bright zone. This zone appeared to be an image of oedematous, but viable brain. In the centre of the lesion, in some cases the hypointense zone contained a hyperintense-to-bright spot. Gadolinium (Gd)-enhanced T1w images were qualitatively similar to T2w images acquired immediately after laser irradiation.

Clinical Studies

In most clinical studies, small, deep-seated inoperable brain tumours were selected for ILTT. Two different methods were used to control intra-operatively the laser treatment, namely computer-controlled power delivery and real-time MRI monitoring. In the first method, one or more thermocouples are positioned interstitially at the periphery of the tumour. Laser irradiation is adjusted by a computer-controlled power delivery system in order to maintain a preselected temperature at the thermocouples (Fig. 3) [31, 39]. The

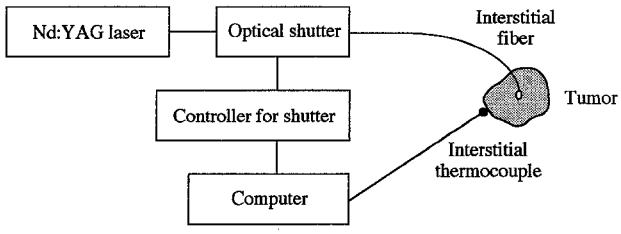

Fig. 3. Computer-controlled power delivery system

patient features and the results of ILTT of both the computer-controlled power delivery studies and the real-time MRI monitoring studies are summarised in Table 1.

Sugiyama *et al.* [39] have treated 5 patients with computer controlled ILTT using a contact probe with a frosted tip. Two thermocouples were positioned in the tissue; one at the periphery and one in the centre of the tumour. The tumours were irradiated at 2–3 W for 30–45 min maintaining the peripheral temperature at 43–45 °C. In 4 out of 5 patients, the tumour diameter was larger than 10 mm, hence multifocal irradiation was performed. All irradiated tumours were reduced in size after 2 to 4 weeks and were disappeared by 8 weeks as noted on the CT scan. In 3 patients, no evidence of tumour recurrence was noted (follow-up 12–34 months) and long-term neurological follow-up revealed no clinical deterioration following ILTT. The remaining 2 patients died: one died of primary lung cancer, the other of a recurrence at the original site, which was not treated by ILTT.

Ascher *et al.* [1] have treated 8 patients with glioblastomas and brain metastases under real-time MRI monitoring. Trepanation was carried out under local anaesthesia and the fibre was inserted under MRI control. The tumours were irradiated at 4 W for 10 min. Further laser irradiation was adapted according to the response of the tumour as seen on MRI. Changes on MRI were first seen after 3 min and consisted of the occurrence of a hypodense region in the centre, surrounded by a hyperdense zone. After 10 min of laser irradiation, a complete loss of the signal occurred in the centre of the lesion. In the first week after laser treatment, the hypersignal at the periphery of the lesion increased in intensity and size on Gd enhanced T1w and T2w images. None of the patients complained of painful sensation during laser irradiation. No additional results or patient follow-up was given.

Roux *et al.* [30, 31] have described ILTT of 6 patients with relatively benign tumours. Two routes were determined in the brain: one for the laser fibre (400 µm bare fibre or cylindrical diffusing tip of 1.68 mm diameter and 10 mm length) and one for the thermocouple which was placed at the periphery of the tumour. Laser irradiation by computer-controlled power delivery was used to maintain the temperature at the periphery of the tumour between 41–43 °C. The laser settings were 3–5 W for 800–1200 s, with a typical distance between the fibre tip and the thermocouple of 10–15 mm. In two cases, multifocal irradiation was performed. In the first day after ILTT, a large central hypodense zone and a peripheral hyperdense zone was observed on T1w MRI. The central hypodense zone increased in size within a few weeks, accompanied by a global retraction of the lesion. Three months after laser treatment, a central hypodense zone corresponding with tissue necrosis was apparent on Gd enhanced T1w and T2w MRI. There was no peri-operative morbidity or mortality.

Kahn *et al.* [3, 4, 20] have treated 16 patients with tumours of 1–3.5 cm in diameter. The tumours were irradiated at 4–5 W for 10–20 min. In some cases multifocal irradiation was performed, depending on the diameter of the tumour. In all patients, the follow-up study with MRI showed a reduction of the tumour size. Only in one patient there was clinical deterioration.

Discussion

In the last decades, there has been great interest in the use of heat for the treatment of cancer. In neurosurgery, radiofrequency, microwaves, and ultrasound have been used to induce hyperthermia [8, 28, 49]. However, one of the main problems in the clinical application of hyperthermia is the distribution of the deposited heat within the tissue. Radiofrequency and microwave heating with external sources cause excessive and irregular heating of the tissue [38]. Interstitial heat delivery provides better heat localisation and distribution than external heating techniques [32]. Therefore, interstitial heating techniques are preferred, such as radiofrequency electrodes, microwave antennas, and implantation of ferro-magnetic seeds activated by an external electromagnetic field [22, 24, 36]. As an alternative to these techniques, ILTT has been developed. Unlike open surgical procedures, this technique is minimally invasive and permits treatment of small, deep-seated intracranial tumours which may otherwise be inoperable.

Clinical studies have demonstrated that ILTT is effective for the treatment of small tumours. All tumours show a response, ranging from total remission to decrease of tumour size, as assessed by CT and MRI follow-up [1, 3, 20, 31, 39]. It is evident that accurate assessment of the extent of the laser induced lesion is of great importance with regard to safe and effective treatment. MRI offers information on localisation, volume and extent of both the tumour and of the laser-tissue interaction [5, 19]. Furthermore, MRI can probably distinguish between reversible hyperthermic changes and irreversible (coagulative) tissue changes. Comparison between MRI and histology suggest that the MRI signal can be used to differentiate between cavitation, haemorrhage, coagulation, dehydration, and oedema, and for localisation of the changes in relation to cerebral structures. Therefore MRI is very promising for monitoring and controlling laser-induced lesions in a clinical setting. This approach is slightly superior to computer controlled ILTT, where the set-up during treatment still has to be considered a black box. Preferably, MRI visualisation of the treatment should be combined with temperature measurements. Various temperature probes that can

Table 1. *Reported Clinical Results of ILTT of Brain Tumours*

Author	Patient	Lesion	Tumour size (Ø in mm)	Location	Laser settings (power; duration)	Fibre	Laser-tissue monitoring	Result (tumour)	Follow-up (months)	Survival
Sugiyama *et al.* (1990)	no. 1	glioma	10-20-15	n.m.	2–3 W; 30–45 min	frosted tip	computer-controlled temperature system	disappeared	34	yes
	no. 2	metastasis	50-34-35	n.m.	"	"		disappeared	32	yes
	no. 3	metastasis	26-24-28	n.m.	"	"		disappeared	11	death
	no. 4	glioma	10-8-12	parietal	"	"		disappeared	23	death
	no. 5	glioma	24-30-25	n.m.	"	"	"	disappeared	12	yes
Ascher *et al.* (1991)	8 patients	glioma WHO II	n.m.	n.m.	4 W; 10 min	ILTT tip*	MRI	n.m.	n.m.	n.m.
Roux *et al.* (1992)	no. 1	fibrillary astrocytoma	25-30-30	3rd ventricle	4–5 W, 15 min	400 µm bare	computer-controlled temperature system	tumour growth; operation + rad. therapy	48 months	yes
	no. 2	astrocytoma	43-35-37	basal ganglia	4 W, 16.5 min	400 µm bare		tumour stable, then growth	22 months	death
	no. 3	astrocytoma	50-38-33	basal ganglia	4 W, 20 min	400 µm bare		tumour stable, then decreased	26 months	yes
	no. 4	oligodendrocytoma grade II	37-28-28	3rd ventricle	2–3.5 W, 7.5 min	diffusing tip	"	tumour growth, worsening	8 months	death
	no. 5	pituitary adenoma	21-19-18	pituitary	2–3 W, 2.5 min	400 µm bare	"	tumour stable	32 months	yes
	no. 6	metastasis of melanoma	15-15-15	thalamus	5–6 W, 17.5 min	400 µm bare	"	tumour growth, worsening	4 months	death
Kahn and Bettag (1994)	no. 1	astrocytoma WHO II–III	18	parietal cortex	4 W; 10 min	ILTT tip*	MRI	small recurrence at the periphery	13 months	death
	no. 2	malignant lymphoma	28	thalamus	5 W; 20 min	"	"	small residual tumour at the border	3 months	death
	no. 3	anaplastic glioma WHO III	27	temporo-parietal	4 W; 15 min (2x)	"	"	disappeared	9 months	yes
	no. 4	astrocytoma WHO II	25	frontal	4 W; 10 min	"	"	no progress	8 months	yes
	no. 5	astrocytoma WHO II	29	frontal lobe	4 W; 20 min	"	"	no progress	10 months	yes
	no. 6	anaplastic glioma WHO III–IV	20	corpus callosum	4 W; 17 min	"	"	recurrence at the periphery	6 months	yes
	no. 7	adenocarcinoma metastasis	20	parietocentral	4 W; 20 min	"	"	n.m.	1 week	death
	no. 8	astrocytoma WHO II	34	frontal	4 W; 11 min	"	"	no progress	2 months	yes

n.m. not mentioned. Ø diameter. * *ILTT tip* cylindrical diffusing tip.

be used in combination with MRI are available. As an alternative to MRI we suggest that ultrasound can be used for visualisation of the treatment in the brain albeit after a craniotomy, necessary for contact between the ultrasound probe and the brain. In a study in normal pig brain this approach appeared to be effective and easy to perform [25].

The main limitation of laser irradiation is the risk of damage to normal brain, which is far more important than anything else. Moreover, the lesions in healthy brain tissue have a maximal diameter of only 16 mm when one bare fibre tip is used. The lesions induced in tumour tissue probably will be slightly larger, as the penetration depth of the Nd:YAG laser is greater in most tumours [42, 43]. The maximum diameter of the lesion in tumour tissue that can be coagulated with a single bare fibre irradiation is about 2 cm. Therefore, ILTT is especially of value for small tumours. Larger tumours, with a diameter ≥ 2 cm, can be treated by ILTT using multiple treatments (replacement of the fibre or insertion of multiple fibres) or cylindrical diffusing fibre tips. Simultaneous activation of multiple fibres is much better than consecutive single fibre insertion. Cylindrical diffusers have the advantage that the power of the laser can be increased. A diffusing tip increases the size of the interface between the light source and the tissue. Thus, with an increased power, the irradiance remains within reasonable limits and carbonisation and cavity formation can be avoided.

Although the treatment results of malignant cerebral tumours has improved in recent years, especially with combination treatments of surgery and chemotherapy or radiotherapy, the survival rates are still unsatisfactory. This is particularly due to the presence of (multi)focal recurrence of the tumour [2, 48]. Therefore, besides optimisation of destruction of the tumour cells at the tumour margins, the use of combination therapies should be considered. A synergistic effect of hyperthermia and radiotherapy is reported by various authors in experimental and clinical studies [35, 36]. Another promising possibility is ILTT in combination with chemotherapy. ILTT causes tissue alterations in the periphery of the lesion. The broken blood-brain barrier as reported by various studies offers the possibility to administer local or systemic antitumoural drugs. The rationale for the use of ILTT in combination with chemotherapy is the observation that hyperthermia increases the cytotoxicity of various chemotherapeuticals by enhancing the uptake of the agents as well as by inhibition of repair of chemically induced lesions [13, 23]. However, insufficient data are currently available on the toxicity of chemotherapy of normal cells under hyperthermic conditions. Therefore, investigations of biological effects of heat combined with chemotherapy on both normal and malignant tissues is needed.

ILTT is minimally invasive and permits treatment of deep-seated intracranial tumours. By a stereotactical procedures, nearly every tumour can be reached which offers at least a palliative treatment. The minimally invasive character of ILTT permits treatment under local anaesthesia [1]. Therefore, this technique may be considered for patients whose condition does not allow general anaesthesia. Furthermore, ILTT can be performed repeatedly and at different sites in the brain, offering advantages above chemotherapy, radiotherapy or externally applied hyperthermia. The only selectivity of laser irradiation for tumour destruction is due to the spatial positioning of the fibre. It is most unlikely that useful selectivity between tumour and normal tissue result from using the same temperature for the same exposure time. Thus ILTT will only be of value in the brain for well defined tumours (e.g., roughly spherical metastases, primary intracranial tumours in inaccessible sites for surgery, and some low grade malignant gliomas). It is probably useless for any infiltrating tumours, where tentacles of tumour are invading normal brain. The first clinical results are encouraging, but longer follow-up times are required to determine the value of ILTT as a curative treatment. Further investigations should include the efficacy of ILTT in animal tumour models, alternatives to the Nd:YAG laser like diode lasers, techniques of delivery, and different imaging modalities of laser-tissue interaction. These studies should optimise the ILTT, which could play a specific role in neurosurgery in the future.

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