5 Laser-Induced Thermotherapy

Birger Mensel, Christiane Weigel, Norbert Hosten

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5.1 Introduction

Laser-induced interstitial thermotherapy is a method for controlled tissue destruction. Cells compounds are destroyed in situ by hyperthermia. Laser-induced thermotherapy (LITT) is able to induce a circumscript necrosis in targeted tissue while maximally surrounding tissue. The first patients were treated 20 years ago and possible gains in therapy of oncologic patients were quickly recognized. LITT has gained broad clinical acceptance in numerous centers during the last 10 years. Advantages of LITT in the treatment of cancer patients are the minimally invasive nature of LITT with percutaneous tissue access under image guidance; the limited investment in hardware and the limited time necessary for a treatment; the possibility of treating patients in analgo-sedation, thus minimizing hospitalization; and the possibility of treating patients after other therapeutic options have failed. The database today is broadest for liver tumors; metastases, foremost of colorectal carcinoma and hepatocellular carcinoma, are tumors treated in large numbers. Lesions in other locations, however, are treated in growing numbers, among them lung tumors, advanced head and neck tumors, renal cell carcinoma, and osteoid osteomas. There is also experience in treatment of brain tumors, prostatic cancer, and pancreatic carcinoma, the latter being of an experimental nature. Modification of the applicators for special indications has broadened the therapeutic spectrum of LITT. LITT is uniquely suited for monitoring by imaging, namely MRI. CT and ultrasound may also be used for some types of thermoimaging, with each of these methods having specific advantages and disadvantages.

5.2 Technical Aspects of Laser-Induced Thermotherapy

The principle of LITT is introduction of laser radiation into tissue while the laser is in contact with tissue. Interaction between laser radiation and tissue results in transformation of laser radiation into thermic energy, which induces three-dimensional coagulation necrosis if the temperature is successfully kept at a thermotoxic level for a sufficiently long time. The diameter of the resulting necrosis depends on the characteristics of the laser used and of the heated tissue.

5.2.1 Physics of Laser Radiation

Laser is an acronym for light amplification of stimulated emission of radiation. Radiation emitted from a laser generator is electromagnetic waves, which are coherent, collimated, and monochromatic. Laser waves are generated in a laser medium by charging processes in the atomic dimension. The charging may be optical, chemical, or electrical. Laser light is generated when charged electrons fall from a higher to a lower level of energy. Energy released during this process is released as light. This process of induced emission results in laser enhancement: a first photon induces the decay of a second photon

of identical phase and wavelength. When certain laser media are being used, laser radiation suited for medical use may result. For LITT, the neodymium:yttrium-aluminium-garnet (Nd:YAG) laser is especially suited. It has a wavelength of 1064 nm, in the near infrared part of the spectrum. The Nd:YAG laser easily transmits energy and is characterized by a high optical penetration into tissue (Roggan et al. 1995).

5.2.2 Interaction Between Laser Radiation and Biological Tissue

At the interface of laser radiation and biological tissue, photons of laser radiation interact with atoms of tissue. Different effects result. Laser light is distributed spatially in the volume it enters. Laser sources with wavelengths in the near infrared part of the spectrum, as they are used in LITT, penetrate deeply into tissue. Optical penetration is on the order of 2–10 mm. Three processes characterize distribution of laser light in target tissue and the resulting effects: absorption, scattering, and bending. Biological effects of laser light are ultimately based on the transformation of laser energy into thermal energy. Photons are absorbed on an atomic and molecular level in different depths of the tissue thus irradiated by laser light. Depending on the thermic capacity of the tissue, a different temperature results. For laser radiation with a wavelength in the near infrared part of the spectrum, absorption is mainly determined by water and hemoglobin content. More generally, the degree of absorption is influenced by laser wavelength and the optical characteristics of tissue. These are described by the absorption coefficient (μ_a), scattering coefficient (μ_s), and the anisotropy factor (g, another parameter describing scattering). On deeper layers of tissue, the proportion of radiation being absorbed decreases (the Lambert Beer law). The amount of thermal energy deposited per volume and ultimately the resulting temperature decreases. During LITT, optical, thermal, and mechanical tissue characteristics change due to heating. Distribution of laser light in these tissues and the gradient of the resulting temperature change (Beuthan et al. 1992; Roggan et al. 1995).

5.2.2.1 Thermal Effects and Tissue Effects

LITT results in heating the tissue volume under treatment. The aim of LITT is complete destruction of malignant tissues. The basic concept of LITT is that of classical hyperthermia, which postulates an increased sensitivity of malignant cells to exposure to heat due to its hypoxic metabolism (Bhuyan 1979). It should be noted, however, that LITT works in a higher temperature range than hyperthermia (60–100 °C). The hyperthermic effect is thus complemented by tissue coagulation. The increase in temperature, which is actually observed, depends not on optical characteristics alone but also on tissue characteristics such as heat capacity and heat convectability).

Thermically induced tissue necroses result from temperature increases beyond 43 °C with the time until cell death depending exponentially on temperature. Locally increased temperature induces a variety of processes, among them induction of enzymes, denaturation of proteins and collagen, and sclerosing of vessels. These phenomena can result in cell death alone or in sum. A carbonization of tissue, however, should be avoided, as it changes optical characteristics of tissue in such a way that laser light is for the most part absorbed, penetration of photons is limited, and the volume of coagulation that can be finally achieved is restricted.

5.2.3 Laser Fibers and Laser Applicators

Transmission of laser energy is achieved by laser fibers (optical fibers). They transmit the visible light and light of the near infrared part of the spectrum with practically no loss and over large distances. Quartz fibers have proven to be well suited for transmission of laser light during LITT. Laser fibers may be destroyed when they absorb part of the laser energy. Quartz fibers are characterized by minimal losses due to absorption for light with a wavelength between 200 and 2000 nm. They are heat-resistant and flexible. They enable near lossless transmission of the high-power density of the laser ray between the laser generator and the laser applicator (Schön-

born 1993). The tip of the laser fibers, which has contact with the tissue under therapy, is modified according to the LITT specification. Applicators of different designs exist, among them ring-mode, bare fibers, and zebra applicators. Cooled diffuser tip applicators have, however, proved most practical for LITT. They are characterized by spherical emission of energy and produce well-defined 3D coagulation necrosis (Steeger et al. 1992; Roggan et al. 1995). Cooled laser applicators differ in their diameter. If the cooling medium is moved in a closed circuit, they have a large diameter because of the need for an inlet and an outlet for the cooling medium, which cools the diffuser tip. If the applicator is open at the tip and the cooling medium allowes vaporizing the diameter is smaller (Hosten et al. 2003; Puls et al. 2003). In the latter design, the cooling medium is pumped through the thin space between the applicator and the laser fiber. Cooling medium vaporizes at the distal orifice of the applicator and ultimately condenses in tissue. Because the space between the laser fiber and the applicator is small, the flow necessary to avoid carbonization may be kept extremely low (0.75 ml/min). The amount of cooling medium needed for a treatment session is thus very small, making recycling unnecessary. The diameter of open-tip applicators is therefore small. Compared to 9F inlet/outlet applicators, the diameter of open-tip applicators may be reduced by 40% to 5.5F (Fig. 5.1). The system may be positioned directly in tissue compared to the Seldinger technique commonly used for applicators with larger diameters. For positioning, a titanium mandrin is introduced into the Teflon applicator, which is replaced by the laser fiber after the applicator is in position. The miniaturized applicator combines the advantages of large diameter, cooled applicators with the smaller diameter of an uncooled applicator. Minimal invasiveness is thus combined with optimized efficacy of laser transmission. Tumors in organs such as the lungs, where invasiveness must be kept to a minimum can thus be treated.

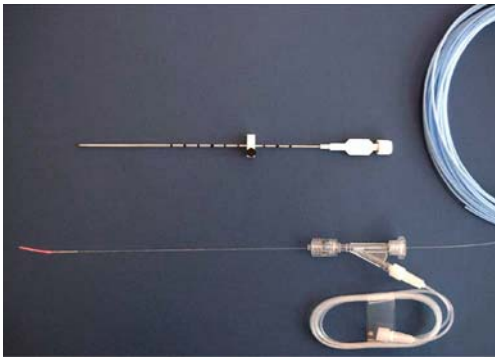

Fig. 5.1 Miniaturized applicator with open tip. The *upper part* shows the applicator with Teflon tubing and the inserted mandrin. After placement of the applicator, the mandrin is exchanged for the laser fiber (*lower part*). The y-shaped distributor connects the Teflon tube to the line that transports the cooling medium

5.2.4 Imaging Temperature Distribution

LITT has the unique advantage of allowing on-line MR thermometry. GRE sequences show signal loss in regions where temperature is increased. There is a correlation between temperature and signal reduction, though whether this reflects temperature or a secondary phenomenon is not clear. Parameter images showing actual isotherms may be generated from MR examinations. This has the advantage that ablation times can be individually chosen, i.e., laser energy is introduced into a metastasis until on-line thermometry demonstrates that the 90 °C isotherm covers the metastasis plus a safety margin of 1 cm. As other ablation therapies do not allow ablation while on-line MR thermometry is performed (radiofrequency ablation) or do not generate phenomena that can be imaged (brachytherapy), other imaging modalities were tried. Ultrasound and CT actually demonstrate some changes in imaging during radiofrequency but whether this is directly temperature-related or corresponds to gas formation is not yet clear.

5.2.5 Application

Laser-induced thermotherapy can be optimized in different ways:

Single-applicator technique. This technique percutaneously places a single applicator; it is removed when therapy is completed. If very large tumors need to be treated, two approaches are possible.

Multiple applicator technique using multiple entries. Between two and five applicators are placed inside one tumor. Heat application is simultaneous. Distances between applicators must be optimized in such a way that applicators are neither burned by neighboring applicators, nor are there low-temperature areas resulting in an insufficient tumoricidal effect. Ideally, a homogeneous ablation zone results, which is larger than that achieved by five single ablations.

Multiple applicator technique using a single entry. For this technique, a single applicator is used for multiple ablations by pulling is back inside the needle tract once ablation at a certain point is achieved. Ideally, a large, oval ablation volume results. Multiple applicators may additionally be pulled back simultaneously (Vogl et al. 2000).

5.3 Laser-Induced Thermotherapy of Liver Tumors

While multiple organs are within the reach of LITT, clinical experience is greatest for metastases to the liver and lungs. Brain tumors have been treated for some time by LITT, while bone metastases and benign bone lesions are more recent targets of clinical research.

5.4 Clinical Results – Laser-Induced Thermotherapy of Liver Metastases

Therapy of primary or secondary liver tumors is a frequent problem in clinical routine. With liver metastases accounting for 90% of all malignant liver lesions, they constitute the biggest challenge. The large number of liver metastases is the result of the liver's role as central organ of Stoffwechsel: it is a filter between the portal and the caval vessel system and therefore prevents malignant cells entering the general circulation. For many tumor entities, liver metastasis is the limiting factor for survival. This holds true especially for gastrointestinal tumors where the liver is the first and often the sole target of hematogenous metastases. Of all patients with colorectal cancer, 25% have liver metastases at the time of diagnosis; 50% develop liver metastases with time. Efficacy of surgical therapy is limited because only 30% of all patients with liver metastases from colorectal primaries can be operated; in more than 50% of all patients with R0 resection, liver metastases recur (Jaeck et al. 1997). All these facts make thermoablative therapies such as LITT so important clinically.

Inclusion criteria for treatment by LITT are a number of lesions not exceeding five (analogous to criteria for surgical resection); no lesion has a diameter of more than 5 cm (technical limit); absence of extrahepatic metastases; relapsing metastasis after surgical resection; metastasis to both lobes of the liver (LITT in combination with surgical removal); and patients whose clinical state does not allow for surgery or who do not consent. Several studies describe results of LITT of liver metastases and hepatocellular carcinoma. Vogl et al. treated 603 patients with 1801 liver metastases in 1555 sessions. They placed the applicators under CT guidance and monitored temperature during ablation by MRI. Local progress after 6 months was observed in 4.4% of patients with tumors measuring more than 4.0 cm, 1.2% for lesions larger between 3.1 and 4.0 cm, 2.4% between 21. and 3.0 cm, and 1.9% for lesions less than 2.0 cm in diameter. Mean survival after diagnosis was 4.4 years (median, 3.5 years) for all patients with 1-, 2- to 3-, and 5-year survival rates of 90%, 77%, 56%, and 37%, respectively. One patient died within 30 days after intervention. Major complications were pleural effusion (17 cases), intra-abdominal bleeding (two patients), liver abscess (n = 6) and one case of pneumothorax, a lesion of the biliary tract, and bronchobiliary fistula each. The study

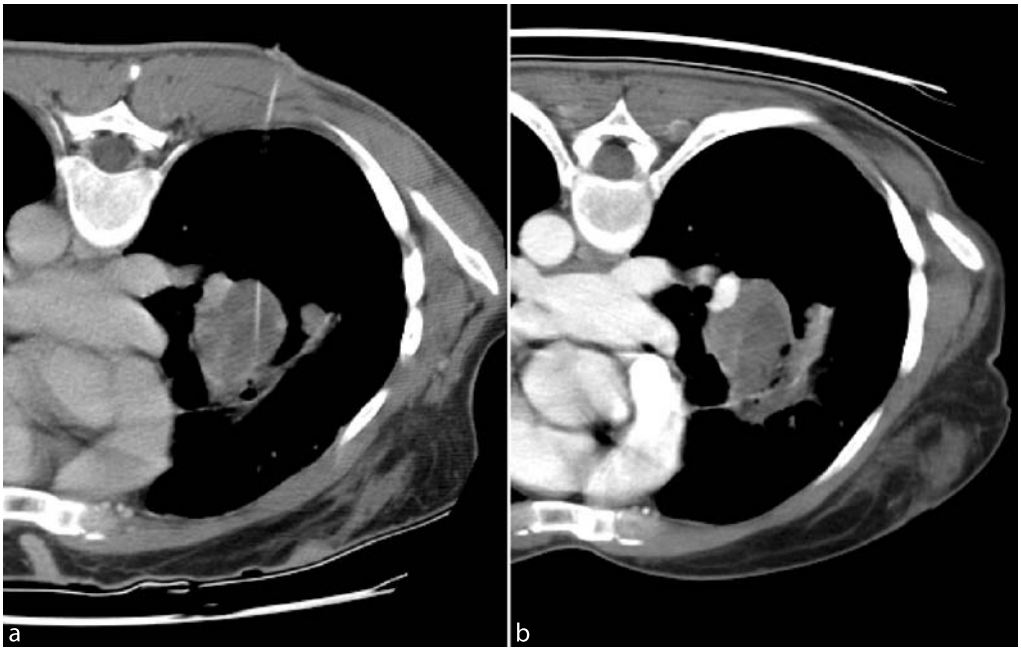

Fig. 5.2 Effect of laser ablation on lung metastases. The *left part* of the image was obtained during LITT with the applicator and the laser fiber in situ. The *right part* was obtained 3 weeks later after infusion of contrast medium. Note that there is an area of reduced perfusion surrounding the laser fiber corresponding to the area, which may be ablated with one applicator in one session. For complete coverage of a lesion of the size shown, multiple applicators can be positioned or a single applicator can be repositioned or treatment can be repeated. The latter option was chosen in this case

also demonstrated that small tumors may be more effectively treated than larger ones; patients treated with cooled applicators preventing carbonization had significantly better survival than those treated with uncooled applicators (Vogl et al. 2004). For 39 patients with hepatocellular carcinoma treated by LITT, Eichler et al. found a technical efficacy of 97.5%. Applicator placement was CT-guided and therapy was performed under MRI monitoring. No major complications were observed (Eichler et al. 2001). A recent paper by our group showed that LITT may safely and effectively treat lesions located close to large vessels in the liver hilum (Mensel et al. 2005). Survival was comparable to that observed after LITT of peripheral liver metastases.

Study design is mainly flawed in patient selection. Prospective, controlled studies could never be performed due to patient preferences. Published studies necessarily include patients treated with a variety of chemotherapies both before and after LITT.

In conclusion, LITT has a technical efficacy greater than 90%. Mortality is less than 0.1%. Mean survival is more than 4 years when patients are selected according to accepted inclusion and exclusion criteria. Frequent complications are pleural effusion and intrahepatic or subcapsular hematoma (Mack et al. 2004; Vogl et al. 2004). Survival rates for LITT are comparable to those after R0 resection, but both mortality and complications are significantly lower. Indications for LITT of liver lesions are more than for operation.

5.5 Clinical Results – Laser-Induced Thermotherapy of Lung Metastases

Our group has performed lung tumour ablation with a thin-caliber laser applicator system with open tip since 2001. Forty-two patients with 64 lung tumors were treated (39 patients with metastases and three with primary tumors). Fourteen lesions were central and 50 were peripheral. Mean follow-up was 7.6 months (range, 6 weeks to 39 months). Eighty percent of treatments were technically successful in the first session. Pneumothorax was the main complication and occurred in 50% of the first 20 patients and in 35% of the rest. Two patients required a chest tube. It took several weeks for the effect of therapy to become apparent on follow-up CT (Fig. 5.2). Thirty-nine percent of all lesions increased in size immediately after treatment. Gross reduction in size with scar formation was seen in 50% of the lesions and cavitations in 13%. Local tumor control was achieved in 51 lesions; 9% of lesions that were less than 1.5 cm progressed despite therapy and progress was observed in more than 11% of larger lesions. Progression was also more frequent in lesions located in the basal parts of the lung (47%).

5.6 Outlook

LITT with an open-tip applicator is suited for the treatment of liver and lung tumors. In lung metastases, lesions located centrally and in the upper parts of the lungs are more easily accessible to treatment than lesions located peripherally and close to the diaphragm. Lesions of medium size show better results than either very small (< 1 cm) or very large lesions (> 5 cm). The open-tip applicator has the potential for infusion of tumoricide substances.

References

1. Beuthan J, Gewiese B, Wolf KJ, Müller G (1992) Die laserinduzierte Thermotherapie (LITT)-biophysikalische Aspekte ihrer Anwendung. Med Tech 3:102–106
2. Bhuyan BK (1979) Kinetics of cell kill by hyperthermia. Cancer Res 39:2277–2284
3. Eichler K, Mack MG, Straub R, Engelmann K, Zangos S, Woitaschek D, Vogl TJ (2001) [Oligonodular hepatocellular carcinoma (HCC): MR-controlled laser-induced thermotherapy]. Radiologe 41:915–922
4. Hosten N, Stier A, Weigel C, Kirsch M, Puls R, Nerger U, Jahn D, Stroszczynski C, Heidecke CD, Speck U (2003) [Laser-induced thermotherapy (LITT) of lung metastases: description of a miniaturized applicator, optimization, and initial treatment of patients]. Rofo 175:393–400
5. Jaeck D, Bachellier P, Guiguet M, Boudjema K, Vaillant JC, Balladur P, Nordlinger B (1997) Long-term survival following resection of colorectal hepatic metastases. Association Française de Chirurgie. Br J Surg 84:977–980
6. Mack MG, Straub R, Eichler K, Sollner O, Lehnert T, Vogl TJ (2004) Breast cancer metastases in liver: laser-induced interstitial thermotherapy – local tumor control rate and survival data. Radiology 233:400–409
7. Mensel B, Weigel C, Heidecke CD, Stier A, Hosten N (2005) [Laser-induced thermotherapy (LITT) of tumors of the liver in central location: results and complications]. Rofo 177:1267–1275
8. Puls R, Stroszczynski C, Gaffke G, Hosten N, Felix R, Speck U (2003) Laser-induced thermotherapy (LITT) of liver metastases: MR-guided percutaneous insertion of an MRI-compatible irrigated microcatheter system using a closed high-field unit. J Magn Reson Imaging 17:663–670
9. Roggan A, Albrecht D, Berlien H-P, Beuthan J, Fuchs B (1995) Application equipment for intraoperative and percutaneous laser-induced interstitial thermotherapy (LITT). In: Müller G, Roggan A (eds) Laser-induced thermotherapy. Spie Optical Engineering Press, Bellingham, pp 224–248

10. Roggan A, Dörschel K, Minet O, Wolff D, Müller G (1995) The optical properties of biological tissue in the near infrared wavelength range – review and measurements. In: Müller G, Roggan A (eds) Laser-induced thermotherapy. Spie Optical Engineering Press, Bellingham, pp 10–44
11. Schönborn K-H (1993) Lichtwellenleiter. In: Berlien HP, Müller G (eds) Angewandte Lasermedizin Lehr-und Handbuch für Praxis und Klinik. ecomed Verlagsgesellschaft mbH, Landsberg-München, pp 1–10
12. Steger AC, Lees WR, Shorvon P, Walmsley K, Bown SG (1992) Multiple-fibre low-power interstitial laser hyperthermia: studies in the normal liver. Br J Surg 79:139–145
13. Vogl TJ, Mack M, Straub R, Eichler K, Engelmann K, Roggan A, Zangos S (2000) Perkutane interstitielle Thermotherapie maligner Lebertumore. Rofo 172:12–22
14. Vogl TJ, Straub R, Eichler K, Sollner O, Mack MG (2004) Colorectal carcinoma metastases in liver: laser-induced interstitial thermotherapy – local tumor control rate and survival data. Radiology 230:450–458