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# Efficacy of Direct Electrical Current Therapy and Laser-Induced Interstitial Thermotherapy in Local Treatment of Hepatic Colorectal Metastases: An Experimental Model in the Rat

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***Background.*** **Local antitumoral therapy of metastases is an important tool in the palliative treatment of advanced colorectal cancer. Several authors have recently reported on successful local treatment of different malignant diseases with low-level direct current therapy. The aim of the present study was to compare the effectiveness of direct current therapy with the established laser-induced thermotherapy (LITT) on experimental colorectal liver metastases.**

***Materials and methods.*** **Colorectal metastases were induced in 49 BD IX rats by injection of colon cancer cells beneath the liver capsule. Three weeks after induction, tumor volumes and sizes were estimated with magnetic resonance imaging and by manual measurement of the largest tumor diameter, and two treatment groups and two control groups were established. Direct current (80 C/cm$^3$) *versus* LITT (2 W; 5 to 10 min) was locally applied via laparotomy. Control groups were sham treated. Tumor growth was analyzed 5 wk after therapy by manual measurement of the maximal diameter and histopathological examination was performed.**

***Results.*** **Measurement of tumor sizes 5 wk after therapy confirmed a significant antitumoral effect of direct current (1.6-fold tumor enlargement) and of LITT (1.3-fold tumor enlargement), compared with controls (2.8-fold and 2.9-fold tumor enlargement). However, after 5 wk, LITT was significantly more effective in limiting tumor growth than direct current treatment ($P \leq 0{,}001$). Histopathological analysis revealed a complete response rate of 21% and a partial response rate of 77% in the electric current group. In comparison, LITT treated livers showed a complete response rate of 22% and a partial response rate of 78% (n.s.).**

***Conclusions.*** **The data confirm that direct current therapy and LITT are effective treatment strategies in the palliative control of colorectal hepatic metastases, with both therapies being equally effective in inducing a complete or partial tumor necrosis.** 

***Key Words:*** **liver metastases; LITT; electric current therapy; electrolysis; electrochemical treatment; colorectal cancer.**

## INTRODUCTION

At the time of diagnosis of colorectal cancer, about 20% to 25% of patients are found to have synchronous liver metastases and an average of 50% of all patients will develop metachronous liver metastases in the course of their disease [1, 2]. The only curative therapy of colorectal liver metastases is surgical resection with reported 5-y survival rates in 25% to 50% of cases [3–5]. Depending on the number of metastases, the location, the volume, the extrahepatic spread, and the overall condition of the patient, complete resection is only possible in 25% of all cases and is associated with a perioperative mortality of 3% to 5% and a morbidity of 20% to 40% [1–4, 6]. If resection is not feasible, a large number of systemic or local palliative treatment options are available. These include systemic and regional chemotherapy [7, 8], intra-arterial chemoembolization [9], cryotherapy [10], alcohol injection [11, 12],

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radiofrequency ablation [13–17], laser-induced thermotherapy (LITT), and low-level direct electric current therapy.

LITT is an encouraging and clinically accepted local antitumoral therapy in the palliative treatment of colorectal liver metastases. To optimize the set-up for the interstitial laser coagulation, different study groups varied the laser power and the overall applied energy, used different fiber tips, multiple fibers, and tried to alter the position of the tip during therapy [18–21]. In animal studies, complete tumor necrosis of colorectal metastases was achieved in 25% to 75% of cases [22, 23]. Primary clinical studies described a complete response rate of 0% to 97% and a partial response rate of up to 87% after LITT of colorectal liver metastases [24, 25]. Long term studies after LITT reported cumulative survival rates of up to 88% at 1 y and up to 42% at 3 y as well as median survival times of over three years in selected patient populations with various numbers and localization of liver metastases [26–29].

An alternative, relatively unknown palliative local antitumoral treatment option is the low-level direct electrical current therapy. The antitumoral effect of electrical current has been known for over 200 years, but was not accepted as clinical standard therapy. Recently, several authors reported promising experimental results after direct current treatment of subcutaneous sarcomas, melanomas, intramuscular implanted hepatomas, and subcutaneous Lewis lung carcinomas. As a result, interest in the electrical current therapy has been renewed [30–33]. Nordenstrom [34] was the first to show the clinical feasibility of low-level electrical current in pulmonary cancer and the first to investigate the biological effects of this therapy on the human organism. Following that, electrical current therapy has become very popular in China, where different superficial and visceral malignant tumors were successfully treated in thousands of patients [35, 36]. Furthermore, promising clinical results have been reported on the treatment of primary liver cancer. However, knowledge of the mechanisms and the biological effects behind the low-level direct current is still too limited for widespread and safe clinical application.

Some animal studies have been published on the treatment of subcutaneously induced colorectal metastases with electrical current [37, 38]. In addition to these experiments, we introduced an experimental model with subcapsularly induced hepatic tumors by injection of a colon cancer cell line. With this experimental set-up we were able to identify optimal treatment modalities and to prove the effectiveness of low level direct current therapy in colorectal liver metastases [39, 40]. However, further information on the effectiveness of low level direct current, especially in comparison with a well established palliative treatment method, such as LITT in colorectal liver metastases, is needed before considering widespread clinical application. Therefore, the objectives of this study were to prove the impact of low level direct current *versus* laser-induced thermotherapy on tumor growth dynamics and on the total outcome after a medium term follow-up period.

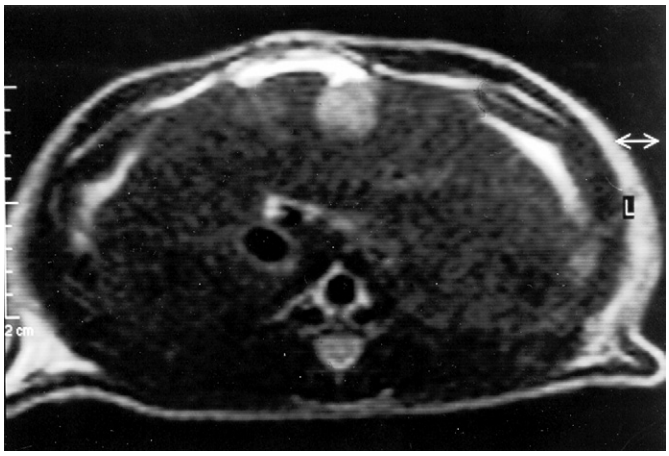


**FIG. 1.** Magnetic resonance image of one induced liver tumor (tumor diameter approximately 5 mm) 3 wk after injection of DHD-K12 cells directly under the liver capsule.

## MATERIALS AND METHODS

### Liver Metastases Model

All experiments described below were approved by the local German government (Bezirksregierung Köln) in accordance with the German law of animal protection (§8 Tierschutzgesetz). Forty-nine syngeneic male BD IX rats were purchased from Charles River GmbH (Sulzfeld, Germany) at age 48 to 54 d with a body weight ranging between 150 and 200 g. They were maintained at a temperature of 22 ± 1°C and a humidity of 55% to 65% with a natural day-night cycle. The animals were provided with commercially available rat chow and tap water ad libitum.

In accordance with Qin *et al.* [41], we used an experimental model with injection of a colon cancer cell line suspension beneath the liver capsule. For this purpose, we used the rat colon cancer cell line DHD-K12/TRb, derived from a 1,2-dimethylhydrazine-induced primary colon carcinoma in the BD IX rat [42]. Tumor cells were cultivated in 75 $cm^2$ cell culture bottles in the culture medium Dulbecco's minimum essential medium (Gibeco, no. 41966-029) with the addition of sodium pyruvate, 5% fetal calf serum, 2% L-Glutamine, 1% penicillin, and 1% streptomycin in an incubator with 9% $CO_2$. After the cells had been removed from the cell culture bottles with trypsin and ethylenediaminetetraacetic acid, a viable cell count was carried out with trypan blue exclusion, whereby the cell concentration was adjusted to $8 \times 10^5$ cells/0.1 mL. Rats where anesthetized with an intraperitoneal injection of ketamine (Ketanest 0.3 mg/kg body weight), combined with xylazine (Rompun, 26 mg/kg body weight). A midline incision was performed to expose the liver, and a 26-gauge needle was introduced directly under the liver capsule. The tumor cell suspension (0.1 mL: $8 \times 10^5$ cells) was injected slowly over a period of 30 s. After removal of the needle, a small piece of collagen fleece was pressed on the point of insertion to prevent bleeding and to avoid spread of tumor cells into the peritoneal cavity. The injections were performed at three to four different liver lobes on the visible liver surface. Finally, the abdominal wall was closed by two layers of running suture.