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# Electromagnetic thermotherapy using fine needles for hepatoma treatment

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## Abstract

*Background and aims*: Hepatocellular carcinoma can be treated with heat-based therapies, especially radiofrequency ablation (RFA). However, RFA has limited efficacy and is quite expensive. We designed a new system using fine needles combined with an alternating magnetic field to generate hyperthermia for the treatment of hepatocellular carcinoma in a rat hepatoma model. Our aims are to assess the efficacy of our method and determine survival up to 30 days.
*Methods*: An N1-S1 cell line was inoculated into the livers of Sprague-Dawley rats, generating tumors after 14 days. The animals were randomized into 5 groups and treated after laparotomy either with normal saline (group I), iron oxide nanoparticles (group II), fine needles (group III), fine needles and iron oxide nanoparticles combined (group IV) or self-designed two-part needles placed under ultrasonographic guidance percutaneously (group V). Every rat was placed in an alternating magnetic field. The temperature in the treatment area was maintained between 55 and 60 °C. At day 30 after treatment, tumor volumes and mortality were assessed and histology samples were studied.
*Results*: Tumor volumes were significantly reduced and survival rate was prolonged in groups III, IV and V versus groups I and II ($P < 0.05$). On pathological examination, groups III, IV and V presented obvious necrosis, apoptosis, calcifications and inflammatory changes in the treatment area.
*Conclusion*: Our study demonstrates that hyperthermia generated by fine stainless-steel needles combined with an alternating magnetic field effectively inhibits hepatoma growth in rats and prolongs their survival. Further, this method can be applied percutaneously under ultrasonographic guidance.

*Keywords:* Hepatocellular carcinoma; Alternating magnetic field; Needles; Rats; Hyperthermia

## Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and the third leading cause of cancer death.[1] Currently, applying heat by radiofrequency ablation (RFA) is a preferred local therapy for patients not eligible for surgery. However, RFA as a heat-based therapy has a number of disadvantages. It is painful, an electrical current circulates through the body, it has a high reported recurrence rate for tumors bigger than 3 cm in diameter[2,3] and it is still an expensive method.[4] Therefore, alternative approaches to deliver heat to HCC tumors have been under investigation.

One of these approaches is the use of electromagnetic fields to generate heat, referred to as electromagnetic thermotherapy. In this modality, a magnetic field is generated through a set of coils which alter the diathermic properties of the tissue or material exposed to it, generating eddy currents that ultimately produce heat. Some authors have reported its use in the treatment of malignancies in vivo.[5,6]

Two main modalities have been tested to deliver electromagnetic thermotherapy to tumors: ferromagnetic nanoparticles and sintered needles.[7–9] Ferromagnetic nanoparticles, originally proposed by Stauffer et al. in 1984,[10,11] have been proven in different studies to be effective when combined with magnetic fields.[12–17] Sintered needles combined

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with a magnetic field were recently reported by Sato et al.[7,17] using a specially designed needle made of magnesium ferrite particles sintered at 1100 °C.

We hypothesize that using stainless-steel needles heated by an alternating magnetic field (AMF) will prove an effective, safe and less expensive method to treat HCC regardless of its size. We have proven in previous publications that by using the same system of AMF and needles we can safely perform bloodless liver resections[18,19] and partial splenic resections in vivo,[20,21] generating coagulative necrosis. Here we test our system in the treatment of HCC and compare it against supraparamagnetic iron oxide nanoparticles (SPION). Our aims are to assess the efficacy of our method and the rate of survival at 30 days in a rat hepatoma model. In order to simulate clinical settings more accurately, we went on to develop a needle for delivering electromagnetic thermotherapy in a closed abdomen by ultrasonographic guidance (USG).

## Materials and methods

### *Experimental design*

The experimental groups consisted of 54 SD rats. Each rat developed HCC tumors from the aforementioned xenotransplant and were randomized into 5 groups (Fig. 1). Groups I to IV received treatment in an open abdomen (Fig. 2b and c) and group V in a closed abdomen (Fig. 2d).

Two weeks after the implantation of the N1-S1 cell line the animals were anesthetized again as described above, and a second laparotomy was performed on groups I to IV to expose the livers and to measure total tumoral volumes using a caliper. For group V the measurements were done by ultrasonography. We used the formula recommended by Carlsson[22]:

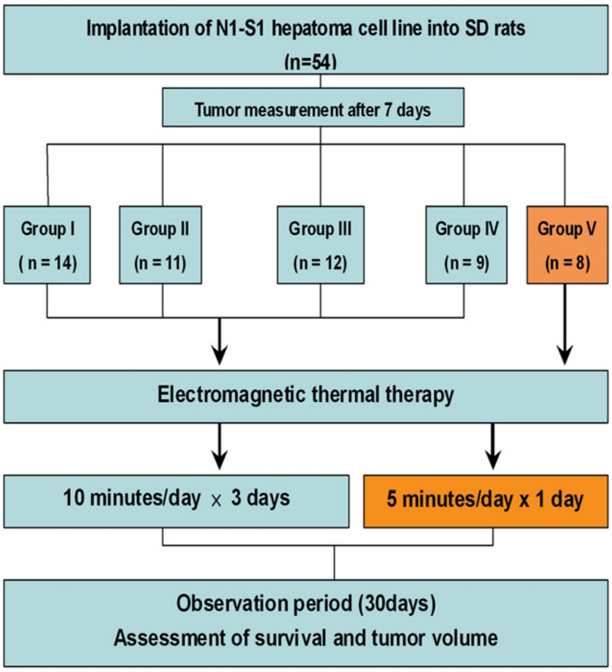

Figure 1. Treatment flowchart. Group I: Normal saline (control); Group II: SPION; Group III: Fine needles; Group IV: Fine needles + SPION; Group V: Two-part needles inserted by USG.

$$V = \frac{axb^2}{2}.$$

where $V$ is the tumor volume expressed in mm$^3$, $a$ is the largest diameter and $b$ is the smallest diameter, both in mm.

The 14 rats of group I received an intratumoral injection of 0.4 ML of normal saline during the second laparotomy to act as a control group. The liver was returned to the abdomen and the incision closed.

Group II, composed of 11 rats, received an intratumoral injection of 0.4 mL of SPION (Fig. 2c) during the second laparotomy, following which they were put under the AMF generator for 10 min. The abdomen remained open in order to continuously measure the tumor and liver surface temperatures. The liver was returned to the abdomen and the incision closed. Each day for the next 2 days the animals were again placed in the AMF generator 10 min, but without re-opening the abdomen.

With the 12 rats in group III, during the second laparotomy we inserted the fine needles into the tumor (Fig. 2b) at 0.5 cm intervals, parallel to the magnetic vector. The total number of needles varied between 1 and 3. This group was placed in the AMF generator for 10 min for 3 consecutive days. On the first day the treatment was applied with an open abdomen to constantly measure the tumor and liver surface temperatures. On the second and third day the needles were left in place inside the tumor and the treatment was applied with the abdomen closed.

Group IV, with 9 rats, received the combined treatments of groups II and III.

For the 8 rats of group V, the two-part needles were inserted by USG (Fig. 2d) at 0.5 cm intervals into the tumors. The AMF generator was applied for 5 min and the needles were removed. The treatment was applied only once because our preliminary data showed the time needed to achieve the desired temperature with this type of needle was lower due to its higher magnetic mass.

For groups II to IV we chose the 10 min interval because we found in preliminary tests this amount of time to be optimal to maintain a temperature between 58 and 60 °C.

For all groups the anal temperature of the rats was measured with a mercury thermometer during every treatment. We monitored each rat for 30 days, after which we again measured the total tumor volumes of the surviving rats, humanely sacrificed by anesthesia overdose, and explanted the livers for histological examination.

### *Cell line*

N1-S1 is a rodent hepatoma cell line derived from Sprague-Dawley (SD) rats, obtained from the Bioresource Collection