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ORIGINAL ARTICLE

# Resistive Part of Impedance as a Possible Indicator of Hepatocellular Carcinoma

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*Background and Aims.* In this work, the multi-frequency impedance both in normal and liver cancer tissues was studied. This was to investigate the feasibility to detect liver cancer by a low cost, easy to use, and a relatively non-invasive electrical impedance measure technique, and thus potentially improving liver cancer diagnosis.

*Methods.* Hepatocellular carcinoma (HCC) was induced in male Wistar rats by the administration of diethylnitrosamine (DEN) during 16 weeks. The electrical impedances at a frequency sweep of 10−100 KHz in the whole body and 10−60 KHz in the liver were taken at the end of the treatment.

*Results.* The electrical impedance showed that the real component values of the impedance change in HCC. In addition, we found that the imaginary component was not associated with HCC.

*Conclusion.* Our results suggest that the electrical impedance may be used as a diagnostic HCC tool. 

*Key Words:* Bioelectrical impedance analysis, Cancer detection, Hepatocellular carcinoma, Resistive electrical component, Tetrapolar arrangement.

## Introduction

Cancer is one of the most important health problems in the world. In 2012, there were approximately 14 million new cancer cases worldwide, and 8.2 million deaths from cancer (1). Hepatocellular carcinoma (HCC) is the main primary liver cancer (70−90% of cases) and has a very poor prognosis, actually more than 90% of the patients diagnosed with liver cancer die. Thus, alternative technologies in the diagnosis and prevention of liver cancer are needed.

In many cases signs and symptoms of liver cancer appear only at late stages. Ultrasound scans, α-fetoprotein levels, spiral computed tomography and magnetic resonance imaging are techniques for the diagnostic of HCC (2). There are also new diagnostic techniques such as electrical impedance spectroscopy that measures the electrical properties of biological tissues (3,4). The first mentioned techniques, requires high-cost equipment, maintenance and highly qualified staff in the hospital, thus the necessary investment is an important barrier to its implementation. In contrast, the measurement of the electrical impedance ($Z$) has gained attractiveness due to its low cost, simple implementation and minimal invasion (5).

The impedance measurement reflects different values in the same biological material due to its internal structure, temperature, concentration of ions and amount of water (6). The electrical impedance of a cell (i.e., the opposition of the cell or tissue to an alternating electric current flow) is measured by its electrical resistance (R) and reactance (Xc) when a high-frequency electrical current of small magnitude passes through it (7). Moreover, the R and Xc values depend on the physiological characteristics of the cell. Thus, the electrical impedance ($Z$) of a cell reflects information on its shape and proportions of intra and extracellular fluids (8,9).

In recent years several works have focused on the distinction between tumor and healthy tissue using

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electrical impedance measurements (EIM) (10−12). For instance, electrical impedance was used in discriminating between brain and tumor tissue *in vivo* by Jahnke H-G, et al. (10). Qiao G, et al. employed EIM to distinguish normal cells from different stages of cancer breast cells (11). EIM in cervical tissue also has been used as a cancer diagnosis by Barrow A, and Wu S, (12). Other experimental approaches have been used to discriminate between cancer and non-cancer cells. For instance, recently, Pallarola D, et al. (13) were able to differentiate breast cancer cells from non-cancer breast cells by studying the cell adhesion properties with nanopatterned indium tin oxide electrodes and electrochemical impedance spectroscopy. Even though there are studies related to the detection of different types of cancer with the measurement of the electrical impedance, to our knowledge, there is very limited or no information on the detection of liver cancer with this technique. Here, we wondered if liver cancer may be detected by bioimpedance measurements carried out with a home-made system specifically designed for electrical measurements of tissues.

## Materials and Methods

### *Animal Experimentation*

Diethylnitrosamine (DEN) was used to induce liver injury in male Wistar rats. This model was chosen because its histological and genetic signatures resemble human HCC. Animal care and procedures conformed to the Institutional Animal Care and Use Committee Guidelines. All animals received humane care. Rats were fed a Purina chow rat diet and water ad libitum. Male Wistar rats weighing 200 g (UPEAL-Cinvestav, Mexico) received intraperitoneal injections of DEN (50 mg/kg) (Sigma Chemical Co., St. Louis, MO, USA) or PBS (control group) once a week for 16 weeks and left two weeks more without treatment to complete 18 weeks, following the procedure described by Schiffer E, et al. (14). With this treatment, the animals developed multinodular HCC. Every week, the body weight of each animal was recorded. The electrical measurements started at the week 12.

Every two weeks, the electrical impedance of each anesthetized rat was measured, and its height and weight were registered (Figure 1A, and B). To induce and maintain anesthesia, the animals were exposed to 4−5 and 1−2% of inhaled isoflurane, respectively. During the electrical measurement, the rats were exposed to an oxygen flow of 0.5−1.0 l/min. At the end of the treatment (i.e., after 18 weeks), the rats were sacrificed with inhaled anesthetic and the liver was chirurgical removed.

### *Equipment*

The main part of the electrical impedance signal acquisition system was the digital signal processor (DSP) (Texas Instrument TMS320F28335) programmed in C++. A

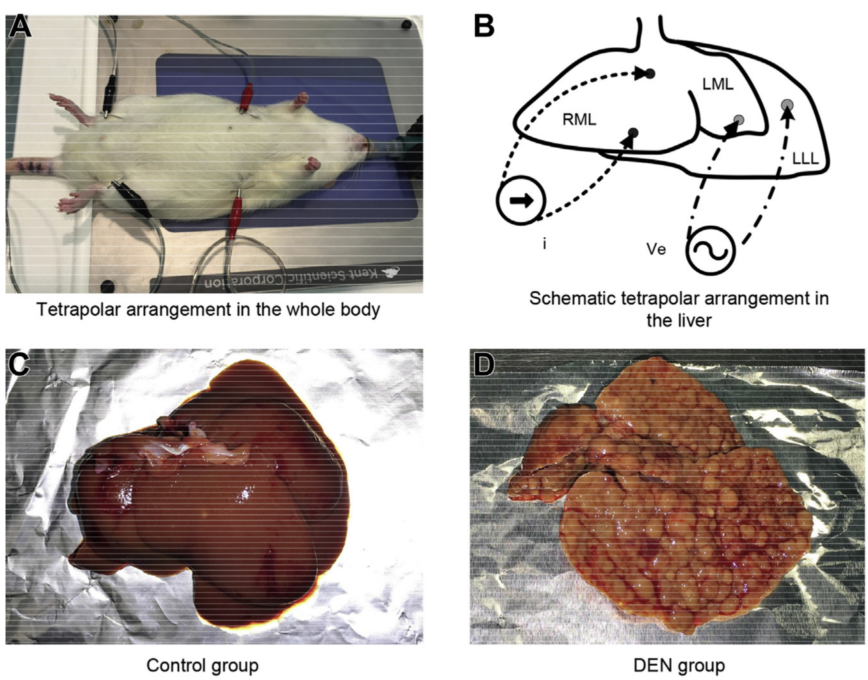


**Figure 1.** Animals and tissues. (A) Anesthetized rat in the supine position with excitation and measuring electrodes in the tetrapolar arrangement. The gray (right) and black (left) clamps hold the excitation and measuring electrodes, respectively. (B) Scheme of the position in the liver of the excitation (i) and measuring (Ve) electrodes. (C) Normal liver tissue obtained from the control group (PBS group), (D) loss of the normal architecture of the liver, and presence of large and abundant HCC nodules (DEN group).