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Patient-specific treatment planning of electrochemotherapy: Procedure design and possible pitfalls

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ABSTRACT

Electrochemotherapy uses electroporation for enhancing chemotherapy. Electrochemotherapy can be performed using standard operating procedures with predefined electrode geometries, or using patient-specific treatment planning to predict electroporation. The latter relies on realistic computer models to provide optimal results (i.e. electric field distribution as well as electrodes' position and number) and is suitable for treatment of deep-seated tumors.

Since treatment planning for deep-seated tumors has been used in radiotherapy, we expose parallelisms with radiotherapy in order to establish the procedure for electrochemotherapy of deep-seated tumors. We partitioned electrochemotherapy in the following phases: the mathematical model of electroporation, treatment planning, set-up verification, treatment delivery and monitoring, and response assessment. We developed a conceptual treatment planning software that incorporates mathematical models of electroporation. Preprocessing and segmentation of the patient's medical images are performed, and a 3D model is constructed which allows placement of electrodes and implementation of the mathematical model of electroporation.

We demonstrated the feasibility of electrochemotherapy of deep-seated tumors treatment planning within a clinical study where treatment planning contributed to the effective electrochemotherapy treatment of deep-seated colorectal metastases in the liver. The described procedure can provide medical practitioners with information on using electrochemotherapy in the clinical setting. The main aims of this paper are: 1) to present the procedure for treating deep-seated tumors by electrochemotherapy based on patient-specific treatment planning, and 2) to identify gaps in knowledge and possible pitfalls of such procedure.

1. Introduction

When a cell is exposed to a sufficiently intense transient external electric field, the permeability of its membrane is increased [1]. This allows molecules that otherwise lack a membrane transport mechanism to enter the cell. Electroporation, as the phenomenon was named, can therefore be used to control the transport of different molecular species in and out of the cell and even induce controlled cell death if the parameters of the electric field are chosen appropriately [2].

Even though the exact molecular mechanisms of electroporation are not yet fully elucidated, it is being used in several medical applications, e.g. electrochemotherapy [3] (which is currently used in daily clinical practice for treatment of superficial tumor nodules in more than 80 clinical centers around Europe [4]), gene therapy [5], and irreversible electroporation (for non-thermal ablation purposes) [6]. Electrochemotherapy combines cancer drugs, such as bleomycin or cisplatinum, with short high-voltage electric pulses, and achieves approximately 80% objective responses irrespective of the histological type of the tumor [7]. When planning electrochemotherapy, we can choose between two possible treatment planning modes: 1) following standard operating procedures with predefined geometry of electrodes based on models to predict electroporation, or 2) patient-specific treatment planning. Electrochemotherapy based on predefined geometries was described for skin tumors [7] and brain tumors [8,9] and several clinical trials are registered and are ongoing [10,11]. The first deep-seated tumors were treated and reported recently with electrochemotherapy and irreversible electroporation using long needle variable geometry electrodes, which clearly demonstrated that patient-specific treatment planning is needed [12–15].

Other electroporation-based therapies are also at the stage of clinical trials. Researchers have considerably increased the efficacy of electroporation-based gene transfer for gene therapy and DNA vaccination [16–19]. Furthermore, irreversible electroporation has been demonstrated in prostate, liver and brain *in vivo* on experimental animals [20] and in patients [21]. As a non-thermal ablation technique,

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irreversible electroporation can be used to cause cell death while preserving extra-cellular tissue scaffolding [22], which greatly facilitates tissue healing after tissue ablation.

To bring the benefits of all these electroporation-based therapies to patients, treatment planning (predefined geometry-based or patient-specific) is necessary. By taking into account the patient's anatomy and numerically predicting the electroporation effects of the high-voltage electric pulses, optimal position of the electrodes can be determined, thereby assuring adequate electroporation of the tumor and limiting electroporation of the healthy tissue. We have taken radiotherapy treatment planning, that has been of paramount importance in the success of radiotherapy in the last 50 years, as the basis for the design of treatment planning in electrochemotherapy. We have already demonstrated in a proof-of-principle study [15] that anatomically realistic computer models of target tissue can be built based on medical imaging and by using finite element modeling for calculating the electric field distribution in the tissue, an efficient treatment plan can be prepared for treating deep-seated colorectal metastases in the liver. The main aims of this paper thus are: 1) to present procedures for deep-seated tumors electrochemotherapy based on patient-specific treatment planning, and 2) to identify gaps in knowledge and possible pitfalls of such procedures.

2. Background

Patient-specific treatment planning has been successfully introduced to and is widely used in radiotherapy, which like electroporation is also based on the interaction between a physical agent (radiation in radiotherapy, and electric field in electroporation) and biological tissue [23]. Radiotherapy is a cancer-treatment procedure where energy is deposited locally into the patient's body by a targeted radiation beam. The damage caused by the beam is not tumor-specific; the maximum allowed radiation dose to the tumor is thus limited by the dose the healthy tissue along the radiation path can withstand [24]. The main goal of radiotherapy is to cause enough radiation damage so that tumor cells get permanently inhibited and their growth can be delayed infinitively; therefore, tumor cells cannot proliferate further.

Radiotherapy consists of the following steps: simulation, treatment planning, set-up verification, beam delivery, and response assessment [23], as described in Table 1. Simulation is based on the patient's anatomy; the patient is scanned in order to obtain medical images (using e.g. Computed Tomography – CT or Magnetic Resonance Imaging – MRI) in the same position as expected to be when exposed to the radiation beam. Treatment planning starts by using the acquired medical images for generating a three-dimensional model. First, the target volumes are defined by the radiologist based on the image data in order to calculate the appropriate radiation dose, then the treatment plan is developed by numerical modeling and optimization – mathematical models of radiation damage in biological tissues have been developed in the first half of the 20th century and are, with some adjustments, still used today [25]. After the calculations, the plan is transferred to the controller device that manages the functioning of the irradiating device (e.g. a linear accelerator) that delivers the radiation beam. The set-up verification consists of examining the patient's position (e.g. using laser-based detectors) in order to coincide with the scanned medical images, and to reflect consequently the dose data from the generated treatment plan. Finally, beam delivery is executed and response assessment is performed later on by obtaining a new set of medical images and validating the treatment.

For the purposes of establishing procedures for deep seated tumors electrochemotherapy based on patient-specific treatment planning, we can expose parallels between electrochemotherapy and radiotherapy, as already suggested [8]. In radiotherapy, the radiation dose has to be high enough in the tumor volume to kill all the tumor cells, whereas in electrochemotherapy, the electric field in the tumor volume needs to be sufficiently strong, and the exposure long enough, to cause cell membrane electroporation [12]. Similarly to radiotherapy, electrochemotherapy of deep-seated tumors can also be partitioned into several steps: mathematical model of electroporation, treatment planning, set-up verification, treatment, and response assessment (Table 1). Therefore, in establishing procedure for electrochemotherapy of deep-seated tumors based on patient-specific treatment planning, radiotherapy treatment planning can serve as a well-established example.

The first step of designing electrochemotherapy of deep-seated tumors is to create a suitable numerical model of electroporation, at both cellular and tissue levels by determining material properties (electrical conductivity) as well as electroporation mechanisms that are related to the electric field distribution [26]. After patient-specific data are transferred to the model it can be used in the treatment planning procedure. The treatment planning consists of several phases: image import, image pre-processing, segmentation, three-dimensional model generation, electrode placement, implementation of the mathematical model of electroporation, and optimization of the results: the electric field distribution as well as the number of electrodes and electrodes' positions. The position of electrodes needs to be verified intraoperatively as part of the set-up verification in order to assure the treatment plan is accurately followed. Postoperative response assessment is required approximately 4–8 weeks after the treatment in order to determine effectiveness of electrochemotherapy by radiological imaging or tumor histology: if the patient is rescheduled for reoperation (as part of a two stage procedure [27]) the metastasis is resected and also histologically evaluated.

Table 1
Parallelism and similarities between radiotherapy and electrochemotherapy of deep-seated tumors.

Radiotherapy	Electrochemotherapy of deep-seated tumors
Simulation – medical imaging (CT or a combination of CT with MR or PET) of the patient	Mathematical model of electroporation: cell- and tissue-level models of electroporation.
Treatment planning: delineation of target volumes, definition of dose constraints, construction of the mathematical model geometry, calculation of a suitable plan by numerical modeling and optimization – number of fractions, position and intensity of the beams	Treatment planning: medical imaging (CT or MR, possible combination with PET) of the patient, delineation of target volumes, construction of the mathematical model geometry, calculation of a suitable plan by numerical modeling and optimization – number and positions of electrodes used, intensity of the used electric pulses
Set-up verification: medical imaging (CT or MRI) is used for verifying the position of the patient and target tissues, in subsequent session lasers and tattoo marks are used together with ultrasound (US) and other imaging modalities	Set-up verification: optimal electrode positions are registered on the original medical images; electrode positions are verified using intraoperative ultrasound (US)
Treatment delivery and monitoring: radiation is delivered according to the treatment plan, while imaging is used to control for breathing movements	Treatment delivery and monitoring: after electrode insertion and chemotherapeutic injection, electric pulses are delivered, current and voltage are measured to control for possible errors during electric pulse delivery
Response assessment: post-treatment measurement of tumor size or biological tumor markers with medical imaging	Response assessment: post-treatment measurement of tumor size or biological tumor markers with medical imaging and/or histology, compared to pre-treatment medical images.