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LETTER TO THE EDITOR

Irreversible Electroporation of Prostate Cancer: Patient-Specific Pretreatment Simulation by Electric Field Measurement in a 3D Bioprinted Textured Prostate Cancer Model to Achieve Optimal Electroporation Parameters for Image-Guided Focal Ablation

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Irreversible electroporation (IRE) of localized prostate cancer (PCA) for curatively intended treatment is still considered experimental, though first study results confirm its high developmental potential as an organ- and function-preserving focal therapy. Current limitations thus far include exact calculation of the ablation field, congruence between tumor localization and extension of the ablation field, and organ confinement of the ablation field with sparing of structures/organs at risk. Van den Bos et al. [1], for example, described the ablation field as being two-to-three times larger than expected and extending beyond the prostatic capsule into the neurovascular bundle with the corresponding risks of stress incontinence and erectile dysfunction. Two important factors are discussed. For one thing, electric field configuration strongly depends on tissue heterogeneity and conductivity [2]. The aging prostate with PCA is a very inhomogeneous tissue or organ (PCA, nodular hyperplasia, inflammatory infiltrates, cysts, prostatoliths, urethra, anatomic zones, and capsule). IRE planning with the NanoKnife system, however, developmentally assumes the target tissue to be homogeneous and not organ specific. This limits individual tissue-texture-related prostate-specific IRE ablation planning. For another thing, a spheroidal IRE field coaxially aligned with the needle electrodes in the longitudinal axis is generated in transperineal grid-directed IRE of the prostate. However, the prostate displays pyramidal-to-spheroid asymmetry. Moreover, PCA is often characterized by multifocal, peripheral, asymmetric, nonspheroidal, and capsule-infiltrating or transmural growth (apex, not capsule). This

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makes it very difficult to adjust the IRE ablation field to tumor and prostate geometry, especially in the peripheral areas. Previous approaches to mathematical pretreatment simulation and intra-interventional monitoring by electrical impedance tomography could not be clinically implemented to solve the problem [3, 4].

Current advancements in medical technology involving the use of 3D procedures and IRE gave rise to the project idea of performing an individual pretreatment simulation of IRE ablation by electric field measurement in a 3D bioprinted model composed of matrix, cells, and possibly anorganic structures with a resulting heterogeneous tissue structure based on patient-specific multiparametric MRI (mpMRI) imaging of the prostate and periprostatic structures. This could enable pretreatment determination of optimal individual IRE parameters for focal, tumor-congruent, organ-confined IRE ablation of PCA as the solution to the above problem. This is achieved by combining three aspects:

First Modern commercially available plastic 3D printers make it possible to create accurate bodies for a wide variety of applications. In the field of medicine, they can be used to make detailed 3D models of patients' organs for preoperative visualization and surgical planning in order to counterbalance disadvantages of the limited depth perception associated with a 2D screen display [5]. In some cases, we use this procedure to counsel patients and plan their treatment for localized PCA with the aid of an mpMRI-based 3D model for patient-specific visualization of the prostate with PCA foci (Fig. 1) [6].

Second In vitro tissue models are useful platforms that can facilitate systematic laboratory investigations of complex culture systems. Bioprinting makes it possible to create highly complex 3D architectures with living cells. Bioprinting techniques have been developed to precisely and rapidly generate patterns of living cells, biological macromolecules, and biomaterials facilitating physiologically relevant cell–cell and cell–matrix interactions. These technologies hold great potential for applications in cancer research [7, 8]. 3D bioprinted organ/tumor models with individual textures could enable pretreatment in vitro simulation of tissue-structure-dependent ablation procedures. The development of a 3D cell culture model for PCA also seems possible [9].

Third IRE ablation uses a series of brief but intense electric pulses delivered by paired needle-like electrodes into a targeted region of tissue, killing the cells by irreversibly disrupting cellular membrane integrity within a localized electric field with a critical potential at about 1500 V/cm or more. This potential can be measured via working electrodes in relation to the distance of the IRE electrodes (Fig. 2). Inactive IRE electrodes placed in the target tissue can also be used as working electrodes to determine the potential of an adjacent active pair of electrodes in that particular area of the target volume (Fig. 3).

Taken together, more individual IRE planning would be possible for focal treatment of localized PCA, and the following simulation approach should be discussed: First,

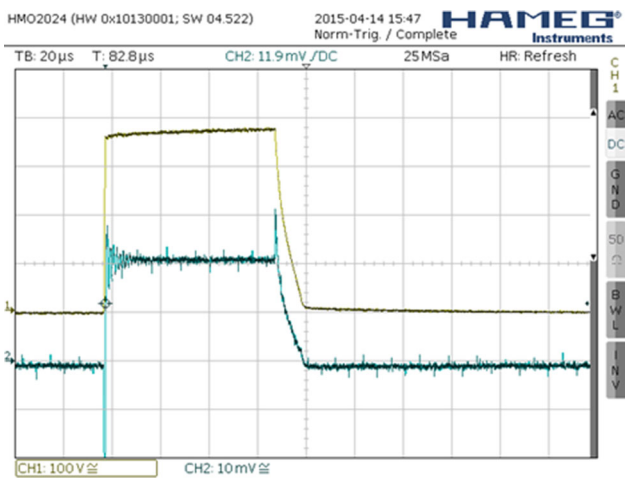

Fig. 2 Graph experimental setup voltage measurement (V) in gel phantom using PF 753, oscilloscope, 2 isolating transformers, and PFO 224 (current clamp): Channel 1 voltage curve IRE electrode (*yellow-black*) and channel 2 voltage curve working electrode (*blue-black*). Distance between IRE and working electrode 20 mm. Different voltage distribution and field strength in the target volume in relation to conductivity (transmission ratio)

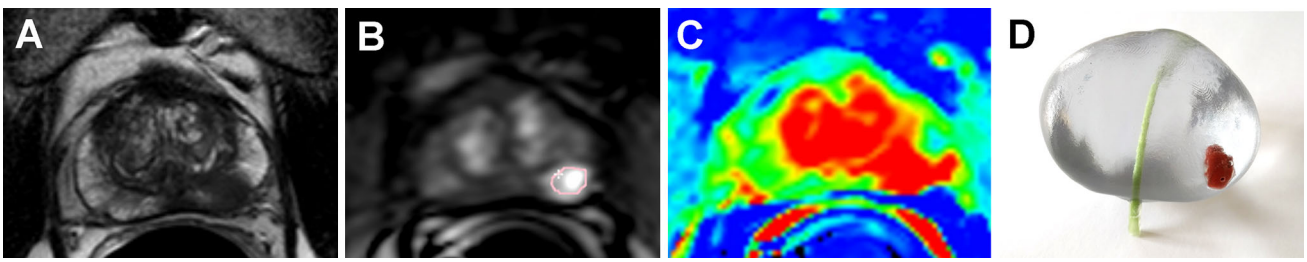

Fig. 1 **A–C** mpMRI prostate transverse view. **D** 3D printed model (rapid prototyping, stereolithography with transparent UV-curable plastic, and colored silicon structures) of a patient-specific prostate based on mpMRI (*left*) with tumor structure (*red*) and urethra (*green*) (Color figure online)

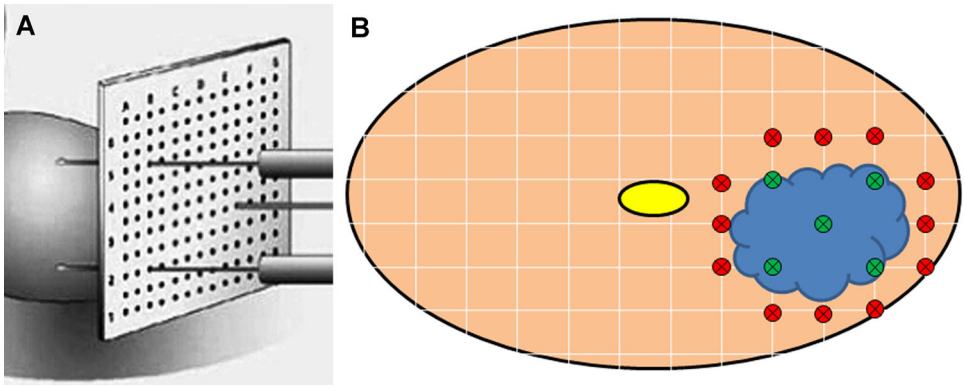

Fig. 3 Diagram IRE prostate/model via template (table of fields or white checkered pattern); prostate in transverse section with urethra (*yellow*) and PCA (*blue cloud*), inactive IRE electrodes (*green*) also utilizable as working electrodes, outer working electrodes (*red*)

creation of an ex vivo 3D biomodel (3D bioprinting) based on individual mpMRI data. This model ideally has the characteristics of the gland to be treated (tissue inhomogeneity, individual tissue conductivity, special structural features, cysts, calcifications, etc.). Template-based ablation simulation is subsequently carried out in this model: after positioning the IRE needles, specific local measurement of the electric potential is performed via the non-conducting needles or working electrodes during pulse emission in the biomodel. Systematic potential measurement via several working electrodes would enable three-dimensional concentric spheroidal determination of the electric field and critical potential. Thus, the optimal IRE ablation parameters (potential and electrode geometry) could be determined prior to treatment. The measurement results are then used to adjust the IRE parameters (potential, electrode geometry for the active pair of electrodes, and ultimately for the definitive ablation). Finally, the experimental approach is translated into the clinical setting.

At present, mpMRI is the imaging technique that provides the most accurate diagnostic and morphologic image data for the prostate and PCA. Current limitations consist in the sensitivity and specificity for PCA detection as well as translation from the morphologic image features of the prostate (texture) into tissue-specific features of the prostate tissue (density, cell–matrix ratio, nucleus–plasma ratio, and conductivity). Further limitations arise from subjective mistakes made by the examiner (interpreting MRI findings, determining outer prostate borders and tumor volumes, and performing a biopsy and histopathological examination) as well as from objective technology-related errors (mpMRI algorithms, image fusion algorithms, and biopsy technique). Corresponding discrepancies between the imaging/evaluation and the true status influence the effectiveness of focal therapies. First comparative analyses have been carried out using 3D printing methods [10]. Automatic segmentation of the prostate and PCA in 3D magnetic resonance images is a challenging task due to the varying shapes, sizes, and textures involved [11]. The introduction and implementation of the above-mentioned principles based on patient-specific data could enable a more precise and reliable IRE application for PCA in the future.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

References

1. Van den Bos W, de Bruin DM, Jurhill RR et al. The correlation between the electrode configuration and histopathology of irreversible electroporation ablations in prostate cancer patients. World J Urol. 2016;34(5):657–64. doi:10.1007/s00345-015-1661-x.
2. Golberg A, Bruinsma BG, Uygun BE, et al. Tissue heterogeneity in structure and conductivity contribute to cell survival during irreversible electroporation ablation by "electric field sinks". Sci Rep. 2015;16(5):8485.
3. Neal RE 2nd, Millar JL, Kavnoudias H, et al. In vivo characterization and numerical simulation of prostate properties for non-thermal irreversible electroporation ablation. Prostate. 2014;74(5):458–68.
4. Kranjc M, Markelc B, Bajd F, et al. In situ monitoring of electric field distribution in mouse tumor during electroporation. Radiology. 2015;274(1):115–23.
5. Takagi K, Nanashima A, Abo T, et al. Three-dimensional printing model of liver for operative simulation in perihilar cholangiocarcinoma. Hepatogastroenterology. 2014;61(136):2315–6.
6. Priester A, Natarajan S, Le JD, et al. A system for evaluating magnetic resonance imaging of prostate cancer using patient-

specific 3D printed molds. Am J Clin Exp Urol. 2014;2(2):127–35.
7. Pati F, Gantelius J, Svahn HA. 3D bioprinting of tissue/organ models. Angew Chem Int Ed Engl. 2016;55(15):4650–65.
8. Knowlton S, Onal S, Yu CH, et al. Bioprinting for cancer research. Trends Biotechnol. 2015;33(9):504–13.
9. Jung V, Saar M, Grobholz R, et al. Development of a three-dimensional primary prostate cancer cell culture model. Urologe A. 2008;47(9):1199–204.
10. Priester A, Natarajan S, Le JD, et al. A system for evaluating magnetic resonance imaging of prostate cancer using patient-specific 3D printed molds. Am J Clin Exp Urol. 2014;2(2):127–35.
11. Korsager AS, Fortunati V, van der Lijn F, et al. The use of atlas registration and graph cuts for prostate segmentation in magnetic resonance images. Med Phys. 2015;42(4):1614–24.