TECHNICAL NOTE / *Interventional imaging*

# Multimodal image-guided electrochemotherapy of unresectable liver metastasis from renal cell cancer



F.H. Cornelis<sup>a,\*</sup>, C. Korenbaum<sup>b</sup>, M. Ben Ammar<sup>a</sup>,  
S. Tavoraro<sup>a</sup>, M. Nouri-Neuville<sup>a</sup>, J.P. Lotz<sup>b</sup>

<sup>a</sup> Department of Radiology, Tenon Hospital, Sorbonne University, 4, rue de la Chine, 75020 Paris, France

<sup>b</sup> Department of Medical Oncology and Cellular Therapy, Tenon Hospital, Sorbonne University, 4, rue de la Chine, 75020 Paris, France

## KEYWORDS

Electrochemotherapy;  
Liver metastasis;  
Cone beam CT;  
Ultrasound;  
Interventional oncology

Similarly to irreversible electroporation, electrochemotherapy is an emerging ablation technique for the treatment of primary and secondary liver tumors [1]. However, unlike irreversible electroporation, which uses ultra-short but strong electrical fields to create permanent and hence lethal nanopores in the cell membrane disrupting the cellular homeostasis [2], electrochemotherapy combines the use of a chemotherapeutic drug, such as bleomycin or cisplatin, with the application of electric pulses as physical system to facilitate drug delivery to cells [3]. Electric pulses are delivered between several peripheral and central electrodes as well as between the peripheral electrodes in order to deliver drug to the entire tumor and obtain safety margin [4]. Electrochemotherapy of liver metastases has been showed feasible, safe and effective in phase I/II studies during open surgery but few procedures have been performed under computed tomography (CT) guidance [4,5]. In order to facilitate the procedure when access angles are challenging or for lesions that are hardly visible, the use of combination of electromagnetic tracking and cone beam CT (CBCT) may provide registration of 3D datasets for real-time localization with ultrasound [6,7].

The purpose of this technical note was therefore to demonstrate the feasibility and efficacy of percutaneous electrochemotherapy of liver metastasis performed under multimodal imaging guidance.

\* Corresponding author.

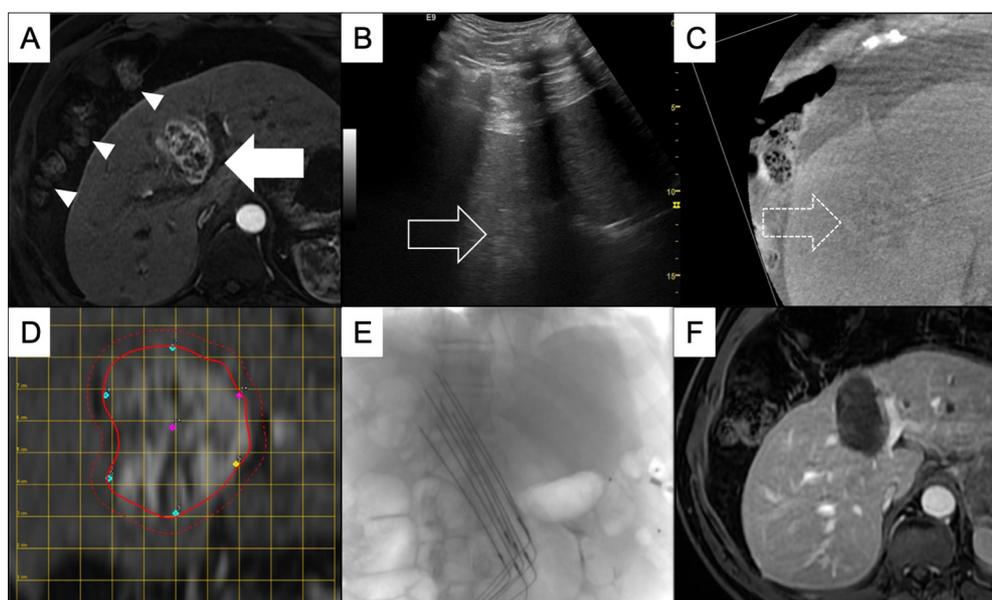
E-mail address: francois.cornelis@aphp.fr (F.H. Cornelis).

## Case description

A 49-year-old man had previously undergone right total nephrectomy 2 years before for a single renal cell carcinoma. He was referred to us to the treatment of a single metastasis in segment IV of the liver. The metastasis was located between the portal and main hepatic veins (Fig. 1A). Due to its direct contact with veins, the metastasis was considered unresectable. Targeted therapies and immune therapies were introduced but MR imaging showed rapid progression of the lesion to 41 mm of maximal diameter. In order to control tumor growth, a local treatment was considered [8]. Conventional ablation techniques such as radiofrequency ablation, microwave ablation or cryoablation were not considered as an option due to the location of the tumor [2]. Electrochemotherapy was thus discussed in multidisciplinary team meeting as salvage therapy and the patient accepted the treatment plan.

Electrochemotherapy was performed under general anesthesia. In order to obtain an adequate insertion of electrodes to cover the whole tumor, a multimodal imaging guidance instead of a CT-guided procedure was planned as the patient presented a colonic interposition between the abdominal wall and the liver. To overcome limited visibility and provide the access angles, contrast-enhanced CBCT and image fusion with ultrasound using EM tracking were used concomitantly (LOGIQ E9<sup>®</sup> and Innova IGS 540<sup>®</sup>, GE Healthcare) (Fig. 1B and C). CBCT was obtained after intravenous contrast medium injection, during the portal phase, in order to enhance

the visibility of the tumor. Automated registration between the CBCT and ultrasound images was performed using an image-based and electromagnetic technology (INTERACT<sup>®</sup> Active Tracker). A small metallic device was placed on the patient, close to the ablation area, prior to the CBCT acquisition. After reconstruction, CBCT data were then loaded in the ultrasound machine, and the position of the device in the image was automatically detected. Thanks to electromagnetic sensors integrated in the ultrasound probe, the position of the device on patient's skin was automatically detected, and automatic registration was made between CBCT data and real time ultrasound images. It allowed fast and accurate tumor targeting as the tumor was not visible on ultrasound alone. According to the individualized treatment plan (Fig. 1D), one 20-cm long needle electrode was firstly inserted in the center of the tumor as well as six similar needles around the tumor, parallel to the central needle (Fig. 1E). The needles were 1.2 mm in diameter with 3-cm non-isolated tip length. This disposition allowed to produce a sufficiently intensive electric field encompassing the tumor and a margin of normal tissue. Distance between the probes ranged from 21- to 26-mm. Electric pulses, generated by Cliniporator Vitae<sup>®</sup> (IGEA) and synchronized with ECG, were delivered 8 minutes after intravenous administration of bleomycin with a bolus of 60 seconds (15,000 IU/m<sup>2</sup>, Sanofi). The settings were fixed to produce a 1000 V/cm electric field within the targeted area: number of pulses of 8, duration of pulses of 100  $\mu$ s and voltage ranged from 2100 to 2600V for each combination of needles. Two positions of



**Figure 1.** 49-year-old man who underwent percutaneous multimodal image-guided electrochemotherapy of liver metastasis from renal clear cell adenocarcinoma. A. Preprocedural postcontrast T1-weighted MR image in the axial plane during the arterial phase shows a single metastasis (arrow) located in segment IV of the liver between the portal and the main hepatic veins. Magnetic resonance image reveals colonic interposition (arrowheads) between the abdominal wall and the liver (Chilaiditi syndrome). B. Perprocedural ultrasound partially shows the tumor (arrow). C. Axial fused reconstruction of contrast-enhanced cone beam computed tomography (CBCT) acquisition using electromagnetic tracking of the ultrasound probe allows a three-dimensional visualization of the tumor and adequate needle placement. The dashed arrow shows enhancing metastasis during the arterial phase following contrast material administration. D. Individualized treatment plan, coronal reconstruction of T1-weighted MR images. This disposition allowed to produce a sufficiently intensive electric field encompassing the tumor and a margin of normal tissue. E. Seven needles were inserted under multimodal imaging guidance including ultrasound and CBCT to cover the whole tumor following the individualized treatment plan. F. Postcontrast T1-weighted MR image in the axial plane at 2 months post-procedure demonstrates complete tumor response.

the needles were obtained: one to treat the superficial part of the tumor and one to treat the deeper part along the same axis. Tolerance was excellent, the post treatment period was uneventful without reported side effects except a resolutive liver cytolysis. Hospital stay was 3 days. Complete response was confirmed on follow-up MR imaging performed at 2 months (Fig. 1F). No adverse effects were reported.

## Discussion

Our observation illustrates that electrochemotherapy of liver metastases can be performed safely and effectively even under CBCT and electromagnetic tracking guidance [1]. This is supported by the results of previous studies that showed regressive histopathological changes in liver metastases treated with electrochemotherapy when the needles were adequately placed [9,10]. Electrochemotherapy induces similar changes in the treated area to that observed after irreversible electroporation. Coagulation necrosis and encapsulation of the treated area were observed. Preservation of large blood vessels (>5 mm) and biliary ducts and slow regeneration of the liver parenchyma were also reported. Like irreversible electroporation, these findings suggest that complete ablation by electrochemotherapy of unresectable tumors in the vicinity of large blood vessels may be obtain, without complications. A possible complete regeneration of the ablated area may finally occur.

But although this single metastasis in a difficult location was successfully treated, the described procedure demonstrates the complexity of electrochemotherapy. Several specific steps have to be taken in consideration during electrochemotherapy such as exact treatment planning for electrode positioning and the delivery of electric pulses, meticulous clinical evaluation before injection of bleomycin to detect any contraindications leading to an optimal coordination between radiology and oncology departments, perfect positioning of the electrodes before injection of bleomycin using multimodal imaging if needed, as well as synchronization of electric pulses delivery with electrocardiography for safety reasons [4]. In that case, the insertion of electrodes proved to be feasible and effective using a multimodal approach under CBCT and ultrasound using electromagnetic tracking. This multimodal navigation is more useful when access angles are challenging or lesions have limited visibility [7]. However, implementation of such CBCT-based navigation and electromagnetic tracking requires hardware, disposables as well as training to master these technologies.

In conclusion, local control may be obtained after multimodal image-guided percutaneous electrochemotherapy in the liver. This promising but relatively complex image-guided percutaneous treatment should be considered for patients with no other alternative. Further larger evaluation

is mandatory before drawing definitive treatment decision tree to guide physicians managing patients in this setting.

## Authors' contributions

F.C., C.K., S.T., M.N.N., M.B.A. and J.P.L. contributed to the design and implementation of the clinical research, to the analysis of the results and to the writing of the manuscript.

## Disclosure of interest

The authors declare that they have no competing interest.

## References

- [1] Probst U, Fuhrmann I, Beyer L, Wiggermann P. Electrochemotherapy as a new modality in interventional oncology: a review. *Technol Cancer Res Treat* 2018;17 [1533033818785329].
- [2] Vroomen LGPH, Petre EN, Cornelis FH, Solomon SB, Sri-mathveeravalli G. Irreversible electroporation and thermal ablation of tumors in the liver, lung, kidney and bone: what are the differences? *Diagn Interv Imaging* 2017;98: 609–17.
- [3] Mir LM, Orlowski S. The basis of electrochemotherapy. In: Jaroszeski MJ, Heller R, Gilbert R, editors. *Electrochemotherapy, electrogenetherapy, and transdermal drug delivery*. Totowa, New Jersey: Humana Press; 2000. p. 99–117.
- [4] Edhemovic I, Breclj E, Gasljevic G, Marolt Music M, Gorjup V, Mali B, et al. Intraoperative electrochemotherapy of colorectal liver metastases. *J Surg Oncol* 2014;110:320–7.
- [5] Mali B, Gorjup V, Edhemovic I, Breclj E, Cemazar M, Sersa G, et al. Electrochemotherapy of colorectal liver metastases—an observational study of its effects on the electrocardiogram. *Biomed Eng Online* 2015;14:S5.
- [6] Abi-Jaoudeh N, Kruecker J, Kadoury S, Kobeiter H, Venkatesan AM, Levy E, et al. Multimodality image fusion—guided procedures: technique, accuracy, and applications. *Cardiovasc Intervent Radiol* 2012;35:986–98.
- [7] Sutter O, Fihri A, Ourabia-Belkacem R, Sellier N, Diallo A, Seror O. Real-time 3D virtual target fluoroscopic display for challenging hepatocellular carcinoma ablations using cone beam CT. *Technol Cancer Res Treat* 2018;17 [1533033818789634].
- [8] White ML, Atwell TD, Kurup AN, Schmit GD, Carter RE, Geske JR, et al. Recurrence and survival outcomes after percutaneous thermal ablation of oligometastatic melanoma. *Mayo Clin Proc* 2016;91:288–96.
- [9] Gasljevic G, Edhemovic I, Cemazar M, Breclj E, Gadzijev EM, Music MM, et al. Histopathological findings in colorectal liver metastases after electrochemotherapy. *Bandapalli OR*, editor. *PLoS One* 2017;12:e0180709.
- [10] Edhemovic I, Gadzijev EM, Breclj E, Miklavcic D, Kos B, Zupanic A, et al. Electrochemotherapy: a new technological approach in treatment of metastases in the liver. *Technol Cancer Res Treat* 2011;10:475–85.