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Electrochemotherapy of cholangiocellular carcinoma at hepatic hilum: a case report

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Abstract. – OBJECTIVE: Cholangiocarcinoma (CCA) is the second most common primary hepatic malignancy after hepatocellular carcinoma. The current standard palliative treatment, chemotherapy regimen with gemcitabine and cisplatin, prolongs overall survival only of a few months. Established locoregional therapies are not a curative option or an alternative to surgery in the treatment of CCA. We report a case of a patient affected by a cholangiocellular carcinoma at hepatic hilum treated by Electrochemotherapy (ECT) at our oncologic center.

CASE PRESENTATION: A 71 years old male affected by a CCA at hepatic hilum was treated with ECT according to ESOPE guidelines. No complications occurred during ECT procedure. The patient was discharged after 10 days. The functional MR evaluation at 2 and at 4 months post-treatment showed a significant response without significant post-treatment adverse events. The Computed tomography (CT) assessment after 18 months did not show progression of disease.

CONCLUSIONS: ECT is safe and its use could be suggested as a palliative treatment of advanced neoplastic lesions in which radical surgical treatment is not possible.

Key Words:
Electrochemotherapy, Liver, Cholangiocellular carcinoma, Hepatic hilum, Tumor thrombus.

Abbreviations

LAPC: locally advanced pancreatic cancer; ECT: electrochemotherapy; MR: magnetic resonance; CCA: cholangiocarcinoma; PHCCA: Perihilar-Cholangiocarcinoma; RF: Radiofrequency ablation; MW: Microwave; DWI: Diffusion-weighted imaging; ADC: Apparent diffusion coefficient; VIBE: Volumetric interpolated breath hold examination; W: Weighted; TR: Repetition time; TE: Echo time; FA: Flip angle; AT: Acquisition time; HASTE: Half-Fourier acquisition single-shot turbo spin-echo; FLASH: Fast low angle shot; FP: perfusion fraction; D pure diffusion coefficient: (DP pseudo-diffusion coefficient (DP); DKI: kurtosis derived parameters; MD: Mean of Diffusion Coefficient; MK: Diffusional Kurtosis.

Introduction

Cholangiocarcinoma (CCA) is the second most common primary hepatic malignancy after hepatocellular carcinoma[1]. The 5-year survival of overall untreated CCAs ranges from 0 to 10%[2]. Surgery represents the only chance of long-term survival and cure of CCA at hepatic hilum. The current standard palliative treatment, chemotherapy regimen with gemcitabine and cisplatin, prolongs overall survival only of a few months[3]. Locoregional therapies are not a curative option alternative to surgery in the treatment of CCA[4-7]. Percutaneous or intraoperative thermal ablation of the tumor mass by Radiofrequency ablation (RF) or Microwave (MW) is not indicated because of possible severe thermal injury of main bile ducts, hepatic hilum vessels and duodenum[8].

Electrochemotherapy (ECT) a non-thermal local tumor ablation modality is a promising tool for treatment of deep tumors[8-16]. This ablative technique combines the administration of chemotherapeutic drugs with electric pulses for cell membrane electroporation (EP)[14]. In our previous studies[14-16] we demonstrated the safety and efficacy of the treatment in locally advanced pancreatic cancer (LAPC). Effective and safe treatment of cholangiocellular carcinoma at hepatic hilum and tumor thrombus in portal vessels at hepatic hilum has been recently reported[9,13]. The purpose of this study is to report a case of a 71 years old male affected by a cholangiocellular carcinoma at hepatic hilum treated by electrochemotherapy at our oncologic center.

Case Presentation

A 71 years old male affected by a cholangiocellular carcinoma at hepatic hilum histologically proven was treated by electrochemotherapy on March 2018. Treatment was performed under

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general anesthesia. Patient provided written informed consent to receive ECT treatment and to publish the study results. The patient underwent resection of a nodule in the segment V and intraoperative ECT of a large peri-hilar CCA in two different placements (Figure 1). Treatment was performed according to a preoperative plan developed using the PULSAR software (IGEA S.p.A., Carpi (MO), Italy). The software calculates an optimized placement of the electrodes within or around a predefined area segmented by the user[17]. The software estimates the coverage of the electric field and minimizes the number of electrodes required. The tool provides an estimation of the electric field in the region of interest selected by expert operators by means of approximate calculations giving indication of electrodes configuration, voltage, and distance for each couple of electrodes[17]. ECT was performed on cholangiocellular carcinoma at hepatic hilum intraoperatively (Figure 1), bleomycin was administrated intravenously (15.000 IU/m^2) before the application of electrical pulses to the target area. Electric pulses were applied by needle electrodes with variable geometry using multiple single needle position (IGEA S.p.A., Carpi (MO), Italy); 8 electrodes of 12 mm of diameters, 30 mm of active part and 16 cm of total length (VGD-1230T16) as shown in Figure 1. Cliniporator™ VITAE (IGEA S.p.A., Carpi (MO), Italy) was used to deliver electric voltage according to European Standard Operating procedure of Electrochemotherapy (ESOPE) protocol, with the following parameters: 8 pulses of 100 µs duration, 1000 V/cm, at heart frequency: single pulse for a single relived R-wave (ECG synchronization) was delivered[18]. Electric impulses were synchronized with the ECG for a safe delivery of the electric impulses to pancreas. ECG synchronization was done with Accusync 42 (AccuSync Medical Research Corporation, Milford, CT, USA). Treatment was completed 20 minutes after the end of the Bleomycin bolus.

Magnetic Resonance Imaging with a 1.5T scanner (Magnetom Symphony, Siemens Medical System, Erlangen, Germany) and with gadolinium based contrast agent administration was acquired before Electrochemotherapy, 7 days and 2 and 4 months after treatment. As functional method, Diffusion Weighted Imaging (DWI) was performed with a phased-array body coil. A free breathing axial single shot echo planar DWI pulse sequence parameters were TR/TE = 7500/91 ms; slice thickness = 3 mm; flip angle = 90 degrees, Matrix = 192x192 and FOV = 340x340 mm^2; b value=0, 50, 100, 150, 1000, 1500, 2000 s/mm^2. MR protocol was provided in Table I.

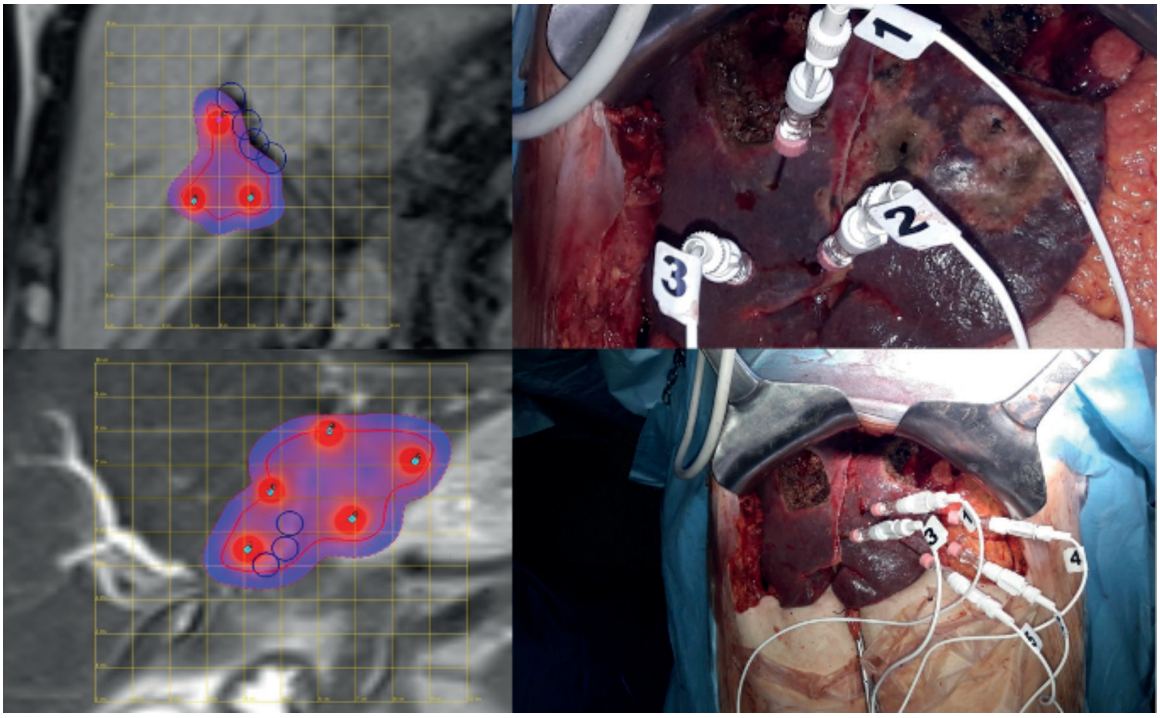

Figure 1. Representative images of preoperative planning and electrodes insertion on operating room.

Table I. MR protocol parameters.

Sequence	Orientation	TR/TE/FA (ms/ms/deg.)	FOV (mm²)	Acquisition matrix	Slice thickness/ gap (mm)
HASTE T2-W	Axial	1500/90/180	380 × 380	320 × 320	5/0
FLASH T1-W, In-out phase	Axial	160/4.87/70	285 × 380	192 × 256	5/0
FLASH T1-W, out phase	Axial	178/2.3/80	325 × 400	416 × 412	3/0
DWI	Axial	7500/91/90	340 × 340	192 × 192	3/0
VIBE T1-W	Axial	4.89/2.38/10	325 × 400	320 × 260	3/0
TWIST T1-W, Pre and post contrast agent injection	Axial	3.01/1.09/25	300 × 300	256 × 256	2/0

W: Weighted; TR: Repetition time; TE: Echo time; FA: Flip angle; AT: Acquisition time; HASTE: Half-Fourier acquisition single-shot turbo spin-echo; FLASH: Fast low angle shot, DWI: Diffusion-weighted imaging; VIBE: Volumetric interpolated breath hold examination.

Per each voxel, 6 features were extracted from DWI data using the mono-exponential approach[19-21], bi-exponential approach (Intravoxel Incoherent Motion method –IVIM)[22,23-26] and the Diffusion Kurtosis Imaging model[26-32].

The parameters of conventional DWI (Apparent diffusion coefficient (ADC), IVIM derived parameters (perfusion fraction (FP), pure diffusion coefficient (D) and pseudo-diffusion coefficient (DP) and DKI derived parameters (Mean of Diffusion Coefficient (MD) and mean of Diffusional Kurtosis (MK) were obtained from the multi-b DWI data with all measured b values using the prototype post-processing software Body Diffusion Toolbox (Siemens Healthcare, Erlangen, Germany). The explanation of these parameters is beyond the scope of this manuscript and for this reason we refer to our previous work[19] and to the lecture of the specific studies[20-31].

The treatment was well tolerated with rapid resolution (5 days) of the abdominal pre-existing pain before ECT. No complication occurred during ECT procedures. No heart abnormalities were reported during EP pulse delivery. The cardiac safety was evaluated based on detected changes in ECG signals recorded during and after surgical procedure. No significant arrhythmias or myocardial ischemia during and after ECT were detected. No clinically significant hemodynamic or serum biologic changes were noted during or following ECT. No bleeding or damage surrounding viscera or vascular structures was reported. The patient was discharged after 10 days. The MR study after 7 days after treatment did not show biliary or vascular lesion due to ECT treatment. A biloma was reported on V hepatic segment due to surgical procedure. The MR evaluation at 2 and at 4 months post-treatment showed a significant response according to functional parameters. Functional evaluation by DWI showed a significant increase of ADC, MD and D and a significant decrease of Fp after 2 and 4 months from treatment; these changes are representative of increase of diffusivity and decrease of perfusion both linked at positive response to treatment (Figure 2). Figure 3 shows the treatment response in terms of lesion dimensional reduction on T2 weighted MR images in coronal plane before (A, B), after 2 months (C, D) and after 4 months

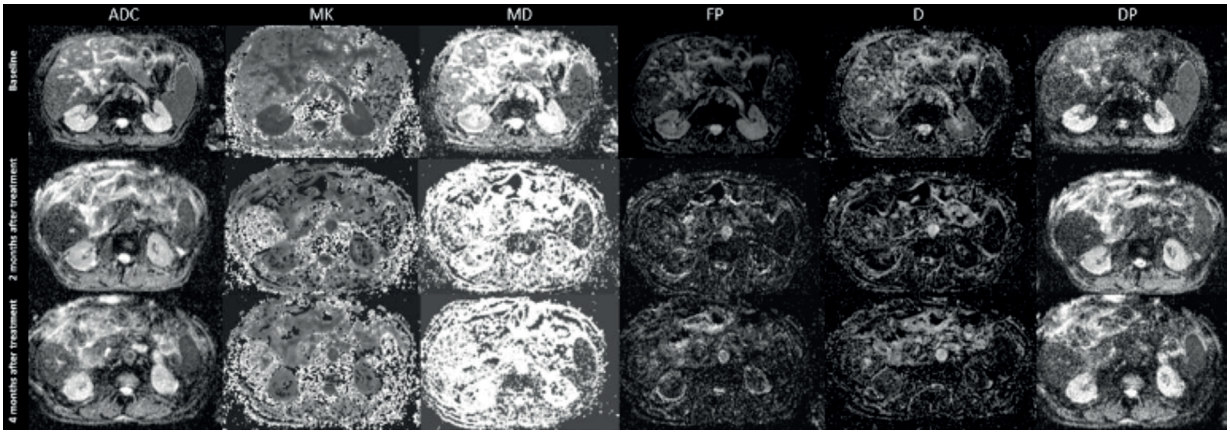

Figure 2. ADC, MK, MD, FP, D and DP maps before, after 2 months and after 4 months from treatment.

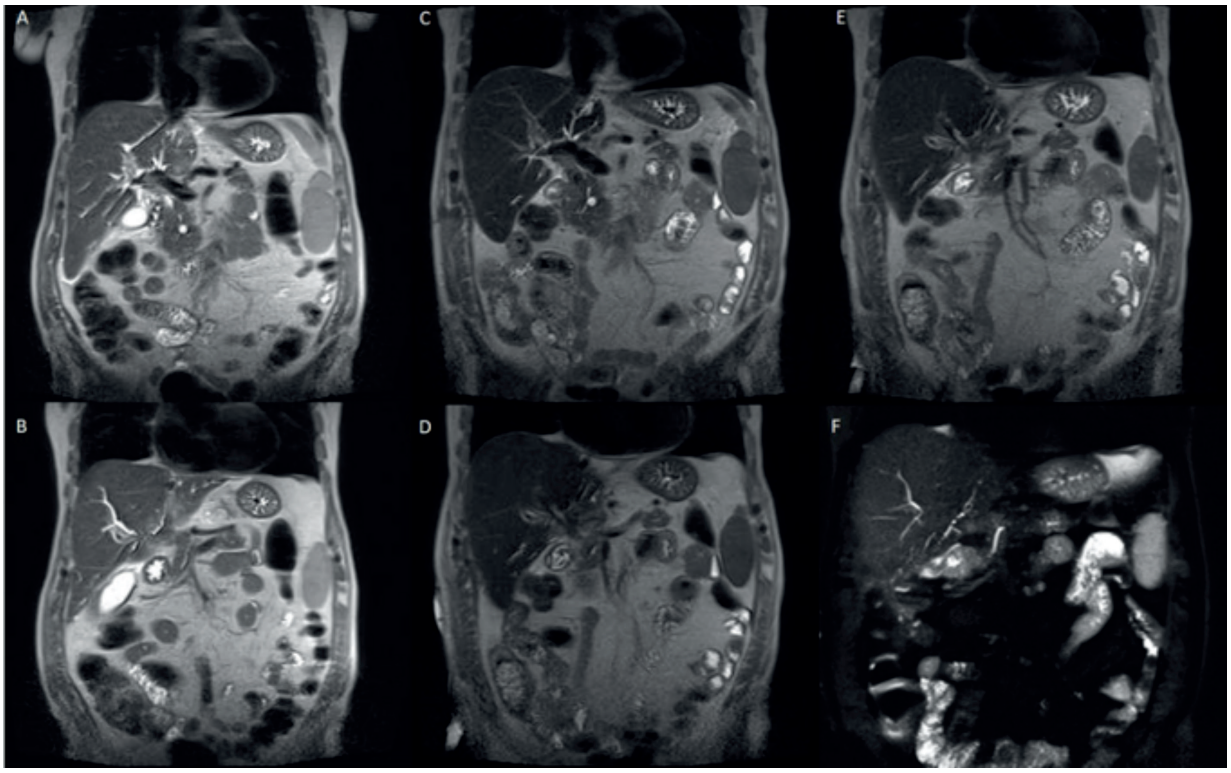

Figure 3. T2 weighted MR images in coronal plane before (**A-B**), after 2 months (**C-D**) and after 4 months from ECT (**E-F**).

from ECT (E, F). Figure 4 shows the treatment response in terms of lesion dimensional reduction on T2 weighted MR images in axial plane before (A, B), after 2 months (C, D) and after 4 months from ECT (E, F). However, the treatment response was assessed quantitatively by means of functional MR derived parameters (Table II) considering the percentage changes between before and after 2 months from treatment (DELTA 1) and between before and after 4 months from treatment (DELTA

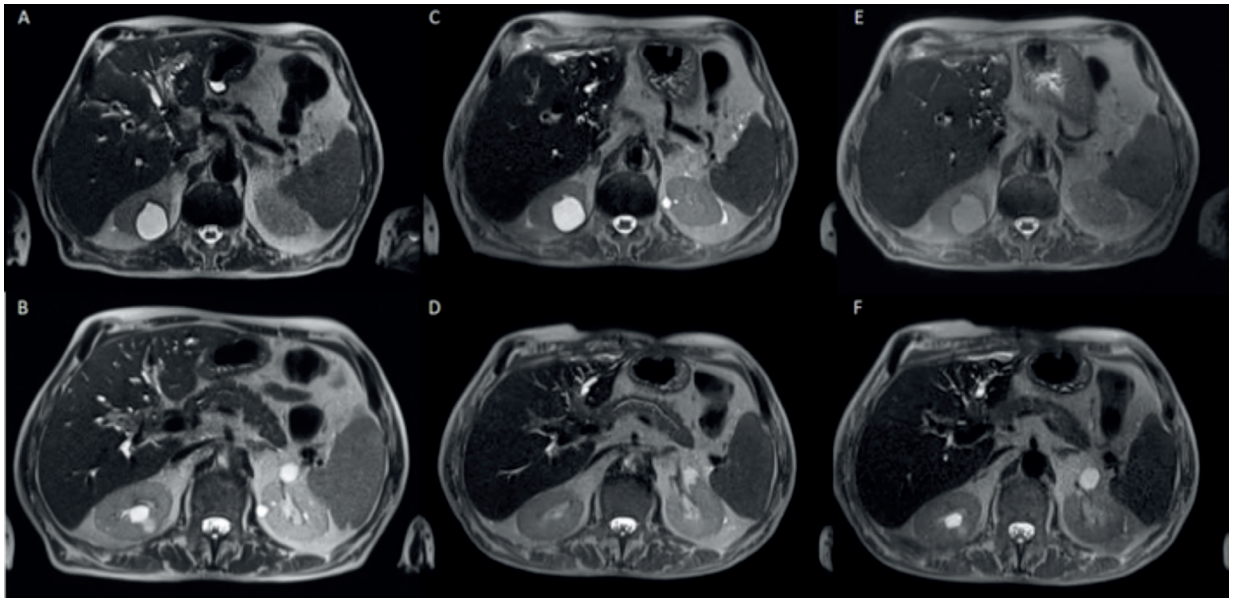

Figure 4. T2 weighted MR images in axial plane before (**A-B**), after 2 months (**C-D**) and after 4 months from ECT (**E-F**).

Table II. ADC, MK, MD, FP, D and DP percentage changes between before after 2 months from treatment (DELTA 1) and between before after 4 months from treatment (DELTA 2).

	ADC (%)	MK (%)	MD (%)	FP (%)	D (%)	DP (%)
DELTA1	13.05	53.53	40.13	-30.56	32.91	184.19
DELTA2	24.87	34.61	47.89	-29.99	47.48	165.29

2). The Computed Tomography (CT) assessment after 18 months did not show progression of disease: no increased tumour size was reported, no new liver or peritoneal metastases were reported, with good performance status of patient.

Discussion

Since the description by Klatskin in 1965[32], the management of patients with tumour of the hepatic bile duct bifurcation has been a challenging clinical problem with a relatively poor prognosis. Complete resection of the tumor with negative histologic margins offers the best possibility of long-term survival, and hepatic resection is a critical component of the operative approach[33]. Chemotherapy regimen with gemcitabine and cisplatin prolongs overall survival only of a few months[3] and locoregional therapies are not a curative option alternative to surgery in the treatment of CCA[4-7]. The benefit of external beam radiotherapy for palliation of proximal cholangiocarcinoma is uncertain[33]. Percutaneous or intraoperative thermal ablation of the tumor mass by radiofrequency ablation (RF) or microwave (MW) is not indicated because of possible severe thermal injury of main bile ducts, hepatic hilum vessels and duodenum[34]. Preclinical studies showed that ECT of liver tumors was well tolerated and devoid of systemic side effects[35]. ECT treatment is a very promising tool in oncological patients[17]. ECT is usually applied as palliative treatment for patients with not resectable lesion, causing an improvement of quality of life. Several researchers have evaluated it as a treatment of advanced neoplastic lesions in which radical surgery is not possible (e.g., due to lesion location, size, and/or number). ECT allows treating lesion in the proximity of vital structures like vessels and nerves. The safety profile of ECT is favourable, with local and transient adverse events[17]. As we reported in our previous studies, the ECT treatment can be used in locally advanced pancreatic cancer with no side effects or major complications to surrounding viscera that required medical or surgical treatment[14,15]. Recently Tarantino et al[13] evaluated feasibility, safety and efficacy of electrochemotherapy (ECT) in 5 patients with unresectable Perihilar-Cholangiocarcinoma (PHCCA). No major complication occurred. Follow-up ranges from 10 to 30 months and confirmed that ECT is feasible, safe and effective therapy to improve prognosis and quality of life of patients with unresectable CCA at hepatic hilum[12]. The feasibility and efficacy of percutaneous electrochemotherapy of liver metastasis was confirmed by treatment performed under multi-modal imaging guidance[36].

ECT induces similar changes in the treated area to that seen with irreversible electroporation, i.e., coagulation necrosis (due to obstructed vessels), and encapsulation of the treated area. However, as suggested by Gasljevic et al[37] some differences exist as demonstrated by preservation of larger blood vessels and biliary ducts and slow regeneration of the liver parenchyma. Peripheral parts of the treated area show regenerative changes 8±10 weeks after the electrochemotherapy. These findings are extremely important when complete ablation of inoperable tumors is performed near large blood vessels.

In our case no major adverse events were reported. No significant arrhythmias or myocardial ischemia during and after ECT were detected. No clinically significant hemodynamic or serum biologic changes were noted during or following ECT. No bleeding or damage surrounding viscera or vascular structures was reported. The patient was discharged after 10 days. According to functional MR parameters the ablated area showed a significant response. The patient to date is alive and the follow up after 9 months reported no progression of disease with good performance status of the patient.

Conclusions

Electrochemotherapy is a safe and effective therapy to improve prognosis and quality of life of patients with unresectable CCA at hepatic hilum, allowing treatment of lesions in the proximity of vital structures like vessels and biliary tree without significant adverse events.

Ethical Approval and consent to participate

Written informed consent to receive ECT treatment and to publish the study results was provided by patient. Ethical approval was not required for a single case report.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Availability of data and materials

All data and materials are provided in the manuscript.

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Authors' Contribution

Dr. Francesco Izzo, Dr. Raffaele Palaia, Dr. Mauro Piccirillo and Dr. Vittorio Albino performed ECT treatment. Dr. Vincenza Granata, Dr. Sergio Venanzio Setola and Dr. Antonella Petrillo performed radiological examination and contributed to biomedical images processing. Dr. Vincenza Granata and Dr. Francesco Izzo wrote the report.

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Conflict of Interests

The authors declare that they have no conflict of interest.

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