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Local treatment with deep percutaneous electrochemotherapy of different tumor lesions: pain relief and objective response results from an observational study

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Abstract. – OBJECTIVE: The aim of this investigation focuses on the evaluation of the efficacy of deep-seated Electrochemotherapy (ECT) in terms of pain relief and local objective response, in pre-treated patients with neither further available pharmacological treatments nor eligible for surgery.

PATIENTS AND METHODS: Deep percutaneous ECT has been performed in 20 patients subjected to systemic anaesthesia. Bleomycin was administrated intravenously before the application of the electrical pulses on the target area, employing multiple single needles depending on the size and location of the target tumor.

RESULTS: Pain assessment based on Visual Analogue Scale showed significant pain relief one month after treatment in all patients, reducing from 7.5 to 3 as a median value (p-value at Wilcoxon test <0.001). Local symptom-free survival median value was 5.5 months. At the first follow-up (1-2 months), a local disease control rate (LDCR) was observed in 19/20 (95%) patients: complete responses in 2 (10%), partial responses in 8 (40%) and stable disease in 9 (45%). Local progression-free survival median value was 5.7 months. Overall, no major adverse effects were observed.

CONCLUSIONS: Our study indicates that deep percutaneous ECT can produce a significant pain reduction and a high LDCR in different tumor lesions, for anatomical site or histotype. In particular, ECT has demonstrated to be effective in various histotypes and deep-seated tumor lesions never treated before by this approach giving a new chance to physicians for reducing oncological pain in patients not eligible to other therapeutic routes. The innovative peculiarity of our study was the successful application of deep percutaneous ECT on adrenal metastasis, malignant pleural mesothelioma, uterine leiomyosarcoma and the uncommon case of a male müllerian tumor.

Key Words:

Deep percutaneous electrochemotherapy, Pain relief, Local disease control, Adrenal metastasis, Malignant pleural mesothelioma, Uterine leiomyosarcoma, Male müllerian tumor.

Introduction

Electrochemotherapy (ECT) is a locoregional anti-tumor therapy that combines a low dose of chemotherapy with high-intensity electric pulses (EP) to induce cell membrane electroporation (EPR) and, consequently, to locally enhance drug delivery into tumoral cells, limiting side effects on normal tissues. Bleomycin and cisplatin are the most used drugs but cisplatin gives the best results in intratumoral administration, while bleomycin can be delivered intratumorally or systemically depending on dimension and number of lesions. This difference is due to the chemical structures of the two drugs, being cisplatin a small neutral molecule with a low membrane permeability and bleomycin a big molecule (MW more than 1400), not permeable to cellular membrane who normally needs copper ions to enter cells. ECT enhances bleomycin all permeability up to 3000 times with respect to standard administration and its pharmacokinetics and safety profile make it the most manageable drug to use in this investigation. Bleomycin is usually administered by intravenous infusion in bolus at a dose of 15,000 UI/m^2 of body surface[1,2].

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ECT has proved to be a safe and effective non-thermal tumor ablation technique against many solid malignancies in all clinical trials adopting the European Standard Operating Procedures of Electrochemotherapy (ESOPE) protocol[3-5] to obtain a local disease control (LDC) in terms of objective response and pain relief. Its effectiveness has been widely demonstrated in several cutaneous pathologies, such as metastatic melanoma[6,7], basal cell carcinoma[8], Kaposi sarcoma[9,10], recurrences from breast cancer[11-13] and head and neck cancer[14,15].

The safety profile of ECT is favorable, with a limited number of adverse events (AE). The most common AE are local effects, including muscle contractions during EPR, edema or erythema, and local pain during and after the procedure. However, according to Quaglino et al[16] there's way to identify subsets of patients at risk of pain at the pre-treatment visit and plan a pain management strategy.

The ECT efficacy and safety, its clinical scope and the recent development of more powerful EP generators and new electrodes have resulted in the first clinical applications of ECT in deep-seated tumors[17,18]. The Standard Operating Procedure developed within the ESOPE Project has already been applied to the non-superficial tumors for the treatment of advanced pancreatic adenocarcinoma[19], bone metastases[20-21], large soft tissue sarcomas[22] and liver metastases[23-26]. Percutaneous ECT has already been used to treat a prospective case series of patients with portal vein tumor thrombus from hepatocellular carcinoma[27] and in patients with unresectable perihilar-cholangiocarcinoma[28].

Based on the encouraging clinical results of the before mentioned studies, we have conducted a clinical study on a population of patients affected by a series of tumor lesions, for different histotypes or deep-seated, with the aims to obtain an improvement of refractory pain and a LDC. In our study, patients were not eligible to further anti-cancer pharmacological treatments and surgery because of technical difficulties (e.g., primary site rectal recurrence already treated with radiotherapy) or non-optimal performance status and impervious deep-seated lesions.

Patients and Methods

End Points and Study Design

Electrochemotherapy was performed according to the ESOPE protocol[3,5]. The internal Ethical Committee approved the study without reserves, together with the module for patients' informed consent (Trial No. 871 of the internal protocol numbering).

Primary endpoint of the study was to assess pain relief of deep percutaneous ECT in the treatment of a miscellanea of deep-seated tumors. Pain control was assessed by means of a pain questionnaire including Visual Analogue Scale (VAS) filled out before treatment (at baseline), one month after, and then, every 4 weeks for the evaluation of local symptom-free survival (LSFS). LSFS was defined as the time from ECT treatment to the date of the first clinical evidence of local pain upgrade or the date of death derived from any cause, whichever occurred first. A low-grade pain corresponded to a VAS value <3, moderate-grade pain to a 3≤VAS<7 value of and high grade to VAS≥7. Secondary endpoint was the achievement of a LDC in terms of local disease control rate (LDCR) and local progression-free survival (LPFS), based on a radiological evaluation of treated lesions by means of modified Response Evaluation Criteria in Solid Tumors (mRECIST)[29]. To be selected as a target lesion within mRECIST, the lesion should meet all the following criteria: (1) the lesion can be classified as a RECIST measurable lesion (i.e., the lesion can be accurately measured in at least one dimension as 1 cm or more), (2) the lesion is suitable for repeated measurement, (3) the lesion shows intratumoral arterial enhancement on contrast-enhanced CT or MRI.

LDCR was evaluated at baseline, at one or two months after treatment and then every three months. Complete response (CR) was considered the disappearance of any intratumoral arterial enhancement in all target lesions, while partial response (PR) corresponded to at least a 30% decrease in the sum of diameters of viable (contrast enhancement in the arterial phase) target lesions, with respect to the baseline sum of the diameters of target lesions. Progressive disease (PD) was translated in an increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, with respect to the smallest sum of the diameters of viable (enhancing) target lesions recorded since the treatment had started. Stable disease (SD) corresponded to any cases that do not qualify for either partial response or progressive disease.

LPFS was defined as the time from ECT treatment to the date of the first radiological evidence of PD in the treated area or the date of death derived from any cause, whichever occurred first.

In addition, LPFS and LSFS was also evaluate by distinguishing the patients with a lesion size (largest diameter) ≤ 4.75 cm from those with a lesion size > 4.75 cm representing the median value of the size of the lesions in our population.

Patients

A total of 20 patients (12 female, 8 male, mean age 65.1 years ranging between 30-83 years) were enrolled. To be included in the study, patients had to fulfil the following basal inclusion criteria: (1) adults (>18 years); (2) life expectancy >3 months; (3) adequate hematologic function (absolute neutrophil count, ≥1500 per cubic millimetre; platelet count, ≥100,000 per cubic millimetre; and hemoglobin level, ≥10 g per deciliter); (4) normal liver function (serum total bilirubin level, ≤1.5 times the upper limit of the normal range); (5) normal renal function (creatinine clearance, ≥50 ml per minute); (6) histologically proven malignant inoperable tumor; (7) previously treated and no further treatment options available; (8) no palliative treatment in place; (9) VAS score ≥ 3.

Exclusion criteria included: (1) age >85 years; (2) pregnant women; (3) significant heart disease; (4) coagulation disorders; (5) hypersensitivity to bleomycin or any of the drugs/components required for anaesthesia; (6) severe lung and/or kidney dysfunction[4,5].

Detailed information about patients and target lesions are shown in Table I. The median value of the lesion size is 4.75 cm (range 2-14). Patients with different histological diseases localized in soft tissue, liver, bone or visceral tumors were admitted to the study, after signing written informed consent.

ECT Procedure

Deep percutaneous ECT treatment was performed in general anaesthesia in all our patients. Anaesthesia was required to manage and alleviate the symptoms both related to the introduction of needles and to the electric pulse delivery. General anaesthesia was performed according to guidelines and to the available drugs in our institution with the principal aim to avoid contractions of the musculature beneath[5].

To access the tumor lesions, individual needle electrodes for variable geometric positioning (VGD series, IGEA, Italy) with either a 3 or 4 cm long conductive part and a diameter of 1.2 mm and 1.8 mm were used. The choice of electrodes depended on the tumor location and size, in particular 1.8 mm diameter for bone lesions and 1.2 mm diameter in soft tissues (Table II). For each treatment, a patient-specific plan was prepared before the ECT procedure, based on cross-sectional Computed Tomography (SIEMENS Sensation Open, Siemens, Erlangen, Germany) images, orthogonal to the electrode access route. Treatment planning was done taking into account the size and location of individual tumors, also with respect to major blood vessels, so that the number and geometrical distribution of the electrodes, their distances, the pairs of electrodes for EPR pulse delivery and the voltages of EPR pulses for each pair of electrodes were accurately calculated and verified. These procedures were performed as previously described[30,31] and were applied by using PULSUR vers. 1.0 software (IGEA, Italy) (Figure 1).

According to the treatment plan, after the insertion of the electrodes into the tumor lesion, the chemotherapeutic drug bleomycin was administered intravenously in bolus at a dose of 15,000 UI/m^2 of body surface. Eight EPR pulses of 100 μs duration in an electric field of 1000 V/cm, were delivered for each pair of electrodes by the EP generator Cliniporator Vitae (IGEA, Carpi, Italy), starting eight minutes after bleomycin administration. Treatment was completed 40 minutes after the end of the Bleomycin bolus according to updated guidelines[5].

As a standard procedure, the delivery of EPR pulses was synchronized with the R-wave of electrocardiogram (ECG) *via* AccuSync 42, an external R-wave-triggering device (AccuSync, USA)[32], acquiring the ECG signal independently from the routine one monitored by the anesthesiologist. In particular, AccuSync 42 detects the R-wave of each heart beat early on the ascending slope of the R-wave, thus providing a trigger pulse to Cliniporator Vitae, which, in turn, delivers EP only after 50 ms, avoiding the so-called vulnerable period of the ventricles (the T-wave). A built-in synchronization algorithm performs validation of all trigger pulses.

In our procedures, synchronization of ECT pulses with refractory cardiac period was performed in all patients except in case of bone localization.

Statistical Analysis

All data were expressed in terms of median value and range. Wilcoxon test was used to verify statistically significant differences in pain, measured by VAS, before and after ECT treatment.

Mann-Witney test was used to verify statistically significant differences between the patient's subgroups. p-value <0.05 was considered significant for all tests. All analyses were performed using Statistics Toolbox of Matlab R2007a (The Math-Works Inc., Natick, MA, USA)

Table I. Patients and target lesion characteristics.

Characteristics	Enrolled patients (n = 20)	%
Gender		
Male	8	40%
Female	12	60%
Median age, years	65.1	Range 30-83
ECOG performance status		
0	2	10%
1	12	60%
2	6	30%
Primitive cancer		
Colorectal	5	25%
Breast	4	20%
Lung	3	15%
• Adenocarcinoma	2	
• Neuroendocrine carcinoma	1	
Pulmonary-Pleura	2	10%
Kidney	2	10%
Melanoma	1	5%
Thymoma	1	5%
Uterine leiomyosarcoma	1	5%
Male mullerian tumor	1	5%
Median size, cm	4.75	Range 2-14
Type of lesion, anatomical site and histotype		
Soft tissue metastases	8	40%
• Pelvis	5	
Colorectal cancer	3	
Uterine leiomyosarcoma	1	
Male mullerian tumor	1	
• Quadricep	1	
Neuroendocrine carcinoma		
• Gluteus	1	
Breast cancer		
• Ileo-Psoas	1	
Colorectal cancer		
Muscle-skeletal metastases	3	15%
• Chest-wall	3	
Malignant pleural mesothelioma	2	
Lung adenocarcinoma	1	
Kidney	2	10%
Clear cell renal carcinoma	2	
Bone metastases	2	10%
• Pelvis	1	
Breast cancer		
• Vertebra	1	
Thymoma		
Lymph nodes metastases	2	10%
• Axilla	1	
Breast cancer		
• Iliac	1	
Melanoma		
Adrenal gland metastasis	1	5%
• Lung adenocarcinoma		
Liver metastasis infiltrating hepatic ductal linked to portal vein	1	5%
• Breast cancer		
Pelvis recurrence from rectal cancer	1	5%

Table II. Treatment characteristics.

Patients	Type of electrode	Active part length [mm]	Number of electrodes
1	VGD-12	30	3
2	VGD-12	30	6
3	VGD-12	30	5
4	VGD-12	30	6
5	VGD-12	30	6
6	VGD-12	30	8
7	VGD-12	30	6
8	VGD-12	30	4
9	VGD-18	30	6
10	VGD-18	30	3
11	VGD-12	30	8
12	VGD-18	30	4
13	VGD-12	30	6
14	VGD-12	40	4
15	VGD-12	30	12
16	VGD-12	30	3
17	VGD-18	40	4
18	VGD-12	30	5
19	VGD-12	30	5
20	VGD-12	20	3

Results

Pain Assessment

Pain was well controlled in all 20 patients. At the diagnosis, 10 patients (50%) suffered from moderate grade (VAS $\geq$ 3 but < 7) and 10 (50 %) from severe pain (VAS $\geq$7). Median VAS for pain was 7,5 (range 6-9) and 3 (range 1-3) before and 1 month after treatment, respectively (p-value at Wilcoxon test <0.001) demonstrating a significant pain improvement (Figure 2). 4-month LSFS was 75%, median value of LSFS was 5.5 months (range 3-10 months) (Figure 3). No statistically significant difference (p-value>0.05 at Mann-Witney test) was observed among the patients with a lesion size $\leq$ 4.75 cm (LSFS median value = 6.5 months) and the patients with a lesion size >4.75 (LSFS median value = 4.5 months).

Objective Response

At the first follow-up, a local disease control rate was observed in 19/20 (95%) patients: complete responses in 2 (10%), partial responses in 8 (40%) and stable disease in 9 (45%); progressive

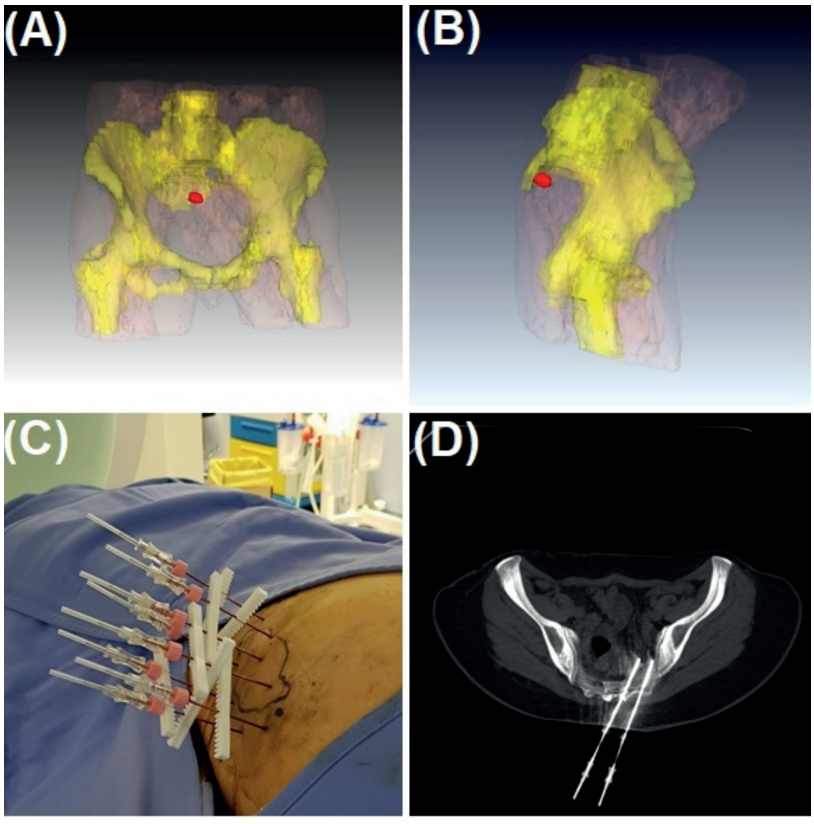

Figure 1. These figures are related to the female patient with uterine leiomyosarcoma pre-sacrum metastasis. **A**, and **B**, show an example of a patient-specific plan prepared before ECT procedure based on cross-sectional 2DCT images orthogonal to electrodes access route. **C**, shows the patient in interventional operatory room with needle electrodes percutaneous inserted into the pelvis, site of the lesion. **D**, represents two needle electrodes inserted into the target.

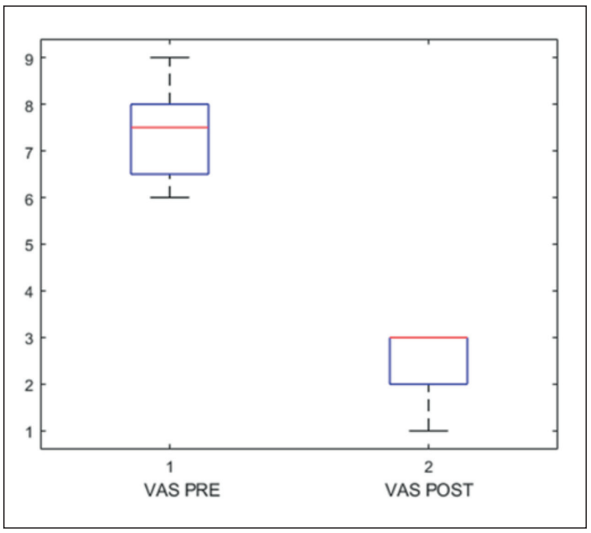

Figure 2. Boxplot of VAS values pre and post-treatment. Pain was well controlled in all 20 patients with a significant pain reduction after ECT from 7.5 to 3 as a median value (p-value at Wilcoxon test <0.001).

disease was seen in 1 (5%) patient (Table III). In Figure 4, an interesting case of complete response in a female patient affected by right clear cell carcinoma is showed.

Median value of LPFS was 5.7 months (range 1-10 months) (Figure 5). No statistically significant difference (p-value>0.05 at Mann Witney test) was observed between ≤4.75 cm (LPFS median value = 6 months) and >4.75 cm (LPFS median value = 4.5 months) lesion sizes.

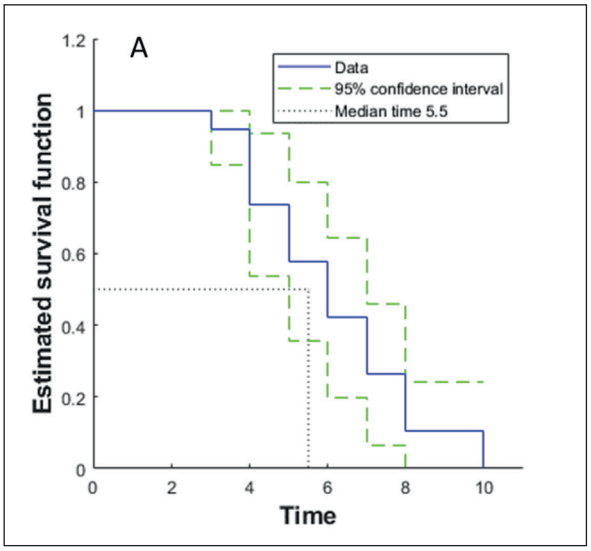

Figure 3. This panel shows Kaplan-Meier estimate of local symptom-free survival (LSFS) in our population (A). LSFS was 5.5 months (range 3-10 months).

Table III. Objective response assessment according to the modified Response Evaluation Criteria for Solid Tumors (mRECIST) at the first follow-up.

Objective response	First follow-up (n =20)	%
CR	2	10
PR	8	40
SD	9	45
LDCR	19	95

The dimension of the target lesions did not influence LDCR, too (p-value>0.05 at Mann Witney test).

Toxicity

Safety was evaluated on the basis of AE, use of concomitant medications, and clinically relevant changes in laboratory values. AE were graded with the use of the Common Terminology Criteria for Adverse Events (CTCAE), version 4.03[33].

All ECT treatments did not trigger serious AE except for limb fatigue in 2 patients (10%), local pain in the treated area in 9 patients (40%) which disappeared after 24-72 hr with mild analgesic treatment and transient increasing of aminotransferases in 1 patient. No fever or nausea were recorded. No re-admissions for fever, pain or other complications were needed. Overall, no major adverse effects were observed.

Focus on Four Tumor Lesions Never Treated Before With Deep Percutaneous ECT

Patient 1

Male, 64-year-old, affected by a right adrenal metastasis from lung adenocarcinoma (EGFR and ALK Wild Type, TPS 30%). At baseline, he had moderate local pain (VAS score 6) and the largest diameter of the target lesion was 4.5 cm. It was contiguous to inferior vena cava, thus not eligible neither to radiotherapy nor to surgery. This patient was excluded from other chemotherapy treatments because of severe iatrogenic toxicity, consisting in Wernicke's encephalopathy following adjuvant chemotherapy. One month after ECT, clinic-radiological assessment demonstrated a pain reduction to VAS score 2, a LSFS of 8 months and an objective response consisting in a PR maintained for 7 months.

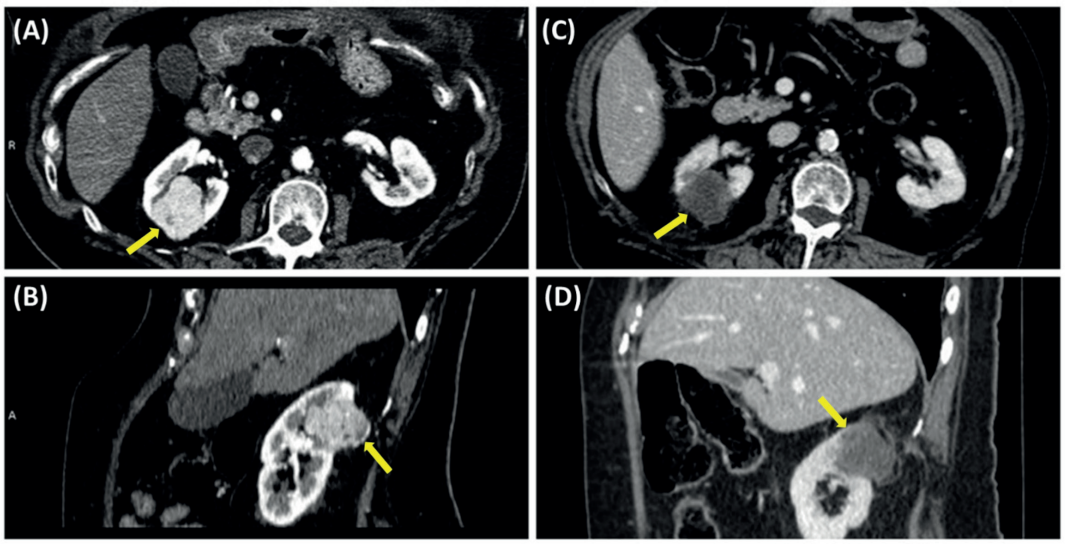

Figure 4. An 83-year-old female affected by right clear cell renal carcinoma subjected to deep percutaneous electrochemotherapy. **A-B**, Baseline Multidetector Contrast Enhancement Computed Tomography (MDCT) showed a tumor lesion in the right kidney (maximum diameter: 50 mm, yellow arrows). **C-D**, According to mRECIST, post-treatment MDCT evaluation demonstrated CR. Please, note the disappearance of intratumoral vascular enhancement in the target lesion.

Patient 2

Female, 57-year-old, affected by soft tissue metastasis in the left paradigma-rectal area from uterine leiomyosarcoma. Before ECT, she had severe local pain (VAS score 7), caused by the target lesion, whose largest diameter was 3 cm. It was deep seated and not suitable for surgery and radiotherapy because of technical difficulties. Moreover, she had already received all available chemotherapeutic options. After treatment, the patient obtained a pain relief (VAS = 3) up to a low-grade, a LSFS of 8 months and a PR for 10 months.

Patient 3

Male, 77-year-old, affected by metastatic involvement of the chest wall from malignant pleural mesothelioma. At baseline, he had severe local pain (VAS score 8) and the largest diameter of the target lesion was 6 cm. He was not eligible to surgery, radiotherapy or systemic chemotherapy because of performance status 3 according to ECOG. One month after ECT, clinic-radiological assessment demonstrated a pain reduction up to a moderate grade (VAS score 2), a LSFS of 4 months and a SD maintained for 6 months.

Patient 4

Male, 83-year-old, affected by an uncommon malignant Müllerian tumor, known as carcinosarcoma, at the left obturator area. Histologically, this tumor is composed of mixed malignant epithelial and mesenchymal elements and usually arises in the uterine corpus or, rarely, in other parts of the female genital tract such as cervix, fallopian tubes, vagina, and ovaries, being uncommon in extragenital sites. This tumor is rare in female and uncommon in male, in

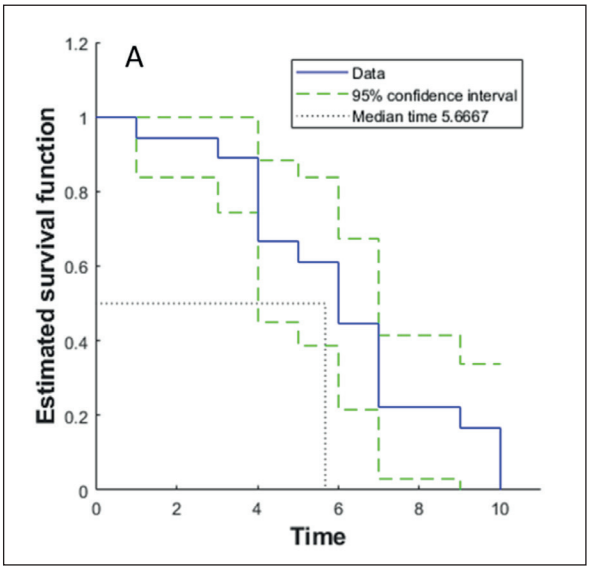

Figure 5. This panel shows Kaplan-Meier estimate of local progression-free survival (LPFS) in our population (**A**). Median LPFS was 5.7 months (range 1-10 months).

fact, only few cases have been described worldwide[34-37]. Our patient complained localized pain in the left groin with propagation to the ipsilateral lower limb, which decreased his quality of life. To manage pain, he had administered large amounts of opioid drugs without a clinical benefit, but with severe side effects, such as constipation and several episodes of delirium. After ECT, he obtained local pain reduction from score 8 to 2 according to VAS and LSFS was 10 months. This patient remained in SD for 9 months and, also in this case, no complications were observed during and after ECT treatment (Figure 6).

Discussion

EPR-based techniques, such as ECT, gene electrotransfection and irreversible EPR, have recently become a viable strategy to treat internal, deep-seated tumors and tissues. In particular, ECT possesses a well-known efficacy in the treatment of cutaneous and subcutaneous tumors and has been applied in a variety of malignant lesions for years[4,38], head and neck tumors included[14,39,40]. These encouraging results have brought clinicians to transfer the acquired experience also in deep-seated tumors. In these cases, access to the treatment area by surgical, percuta-

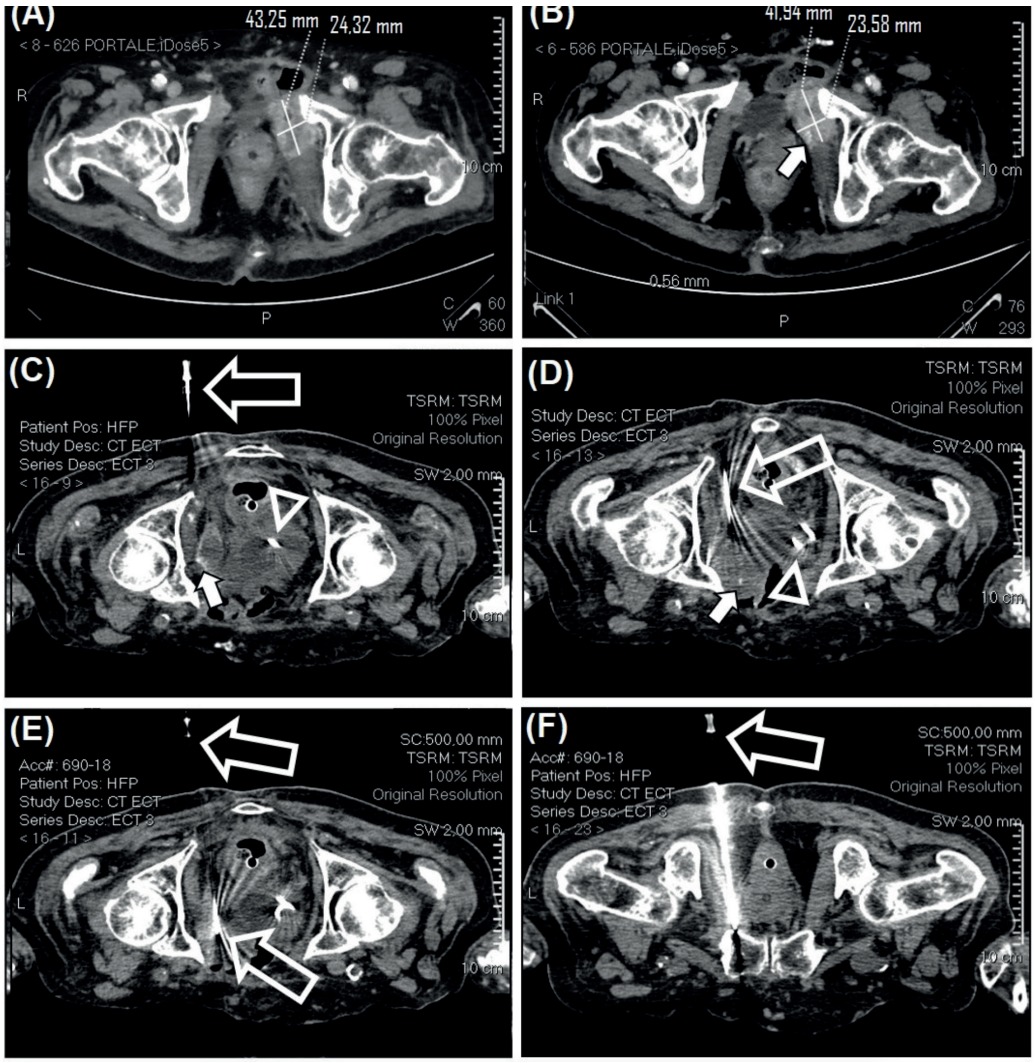

Figure 6. **A**, and **B**, Pre- and post-treatment for male malignant Müllerian tumor, respectively. Please note the lesion, with its diameters, endend up in stable disease. **C**-**F**, perform the sequence of the ECT treatment. Note the typical psammoma bodies of this tumor type *(solid arrows)*. Open arrows indicate the needle electrode that is progressively introduced until the target area. Arrow heads correspond to ureteral stents.

neous or endoscopic procedures is required[18,41,42] and several publications agree in applying ECT according to the Standard Operating Procedure for deep tumors, developed within the ESOPE Project[21-28]. Preliminary results have already demonstrated that ECT treatment of non-superficial organ metastases is possible, effective and safe to obtain pain relief, improvement of quality of life (QoL) and resolution/regression of tumor nodules. To apply a minimally invasive technique, ECT has been also tested to treat small bone metastatic lesions within a phase I-II clinical trial, which has assessed both no clinical complications and patients' fast recovery[20]. MRI evaluation soon after ECT and after 4 weeks showed encouraging results in this particular clinical condition with no standard therapeutic options[20,21]. A two-stage phase II trial enrolling 34 patients affected by advanced soft-tissue sarcomas, showed ECT as an active and safe treatment to achieve tumor control with a local objective response, assessed on 71 target lesions, representing 92.2% of all lesions (with CR 32.3%). Moreover, a LDCR of 72.5% at 2-years was observed after a median follow-up of 19.3 months[22]. Two patients affected by osteoblastic spine metastases involving posterior walls of the lumbar vertebral bodies with epidural extension, were treated with percutaneous ECT obtaining tumor control and improved QoL[23]. ECT was proved to be feasible, safe and effective also in the treatment of colorectal liver metastases in presence of lesions difficult to treat for their position, such as metastases near the major hepatic vessels, not eligible to surgery or radiofrequency ablation[1,23,24,43,44].

ECT has already been used to treat patients with liver cirrhosis and portal vein tumor thrombus from hepatocellular carcinoma[27] and patients with perihilar cholangiocarcinoma, improving their prognosis and QoL[28].

Even though the treatment of deep-seated tumors is now possible with the new EPR device and long-needle electrodes, technological aspects are important to ensure safety to the patients[18], in particular, a precise control of EPR parameters prevents an excessive applied electric current. A specific software called PULSAR[45] calculates both the number of electrodes required to obtain the coverage of the electric field and their right placement within or around a predefined area, segmented by the medical operator.

Since the abdominal tumors, such as liver metastases, are located in electrically high conductive medium and can occupy sites in the proximity of the heart, the delivery of EPR pulses must be synchronized to the refractory period of the cardiac cycle to reduce the risk that electric pulses interfere with heart function[46-48].

Coming to our experience, eleven patients needed cardiac synchronization, no AE were observed during the procedure and subsequent toxic effects were mild and transient, confirming that a well-planned ECT treatment is a useful and safe clinical route, also in highly compromised patients.

Our patients had no other available therapeutic options and suffered from moderate to severe grade local pain according to VAS, responsible for an extensive use of opioid drugs, which were not effective in managing pain, besides determining several side effects, such as hypotension, nausea and vomiting, urinary retention, constipation, respiratory depression and an increased incidence of delirium. Hence, the attempt to set up a new pain management approach to obtain an improvement of refractory pain and, consequently, a reduction in opioid drug intake. As secondary endpoint, the achievement of a LDC evaluated in terms of LDCR and LPFS was fixed. All our patients experienced a significant amelioration in local pain reducing opioid drug intake from 60% to 70% with an overall improvement in their QoL. Moreover, they obtained an excellent LDC.

This study collects a miscellanea of lesions derived from various histotypes and deep-seated lesions. Despite the small sample size, our results support the few published data regarding pain palliation reduction and local tumor control, induced by this approach. Nevertheless, our data go further suggesting that this technique is effective also in tumor lesions never treated before. In fact, to our knowledge, this is the first time that deep percutaneous ECT was applied on thymoma and neuroendocrine carcinoma as well as on deep-seated areas such as axilla, iliac area lymph nodes, pelvic tumoral masses and recurrence from rectal cancer. For the first time in clinics, we used ECT on adrenal gland metastasis, an anatomical site of great clinical interest, and on rare tumoral histotypes, such as malignant pleural mesothelioma, uterine leiomyosarcoma and, above all, the uncommon case of a male müllerian tumor, with optimal results. Our promising results have led us to improve the technique and start a systematic study for a more homogeneous selection of patients and lesions to treat.

Conclusions

We conducted an observational study about the application of deep percutaneous ECT on different deep-seated tumor lesions, for site or histotype. Despite the small sample size, our results indicate that this technique is an effective and safe procedure to improve refractory pain and to obtain local control disease with a significant reduction in opioids intake. Moreover, this is the first ECT successful application on tumoral histotypes, such as thymoma and neuroendocrine carcinoma, as well as on deep-seated lesions, such as axilla, iliac area lymph nodes, pelvic tumoral masses and recurrence from rectal cancer. In particular, the peculiarity of our study was the application of deep percutaneous ECT on adrenal gland metastasis, malignant pleural mesothelioma, uterine leiomyosarcoma and the uncommon case of a male müllerian tumor. Based on these favorable results, we forecast that deep percutaneous ECT will be further tested in an expanded patient population to further support its efficacy in various tumor histotypes and deep-seated masses. From this observational study we obtained important information about the potential of ECT approach where other treatments (opioids for instance) failed, also in terms of patients' compliance that generally more willingly accept loco-regional treatments. Deep percutaneous ECT can be considered an innovative weapon for oncologists to melt old and new therapies to the full advantage of patients.

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Conflict of Interests

The authors have no relevant affiliation or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

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