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Targeted Electrochemical Tumor Therapy by Real-Time Detection and Treatment Probes in Females with Inoperable Chemo/Radioresistant Breast Cancer; A Human Model Study

Abbasvandi F[1,2,3#], Miripour ZS[3,4#], Mahdavi R[3], Mansouri S[4], Jahanbakhsh F[5], Yousefpour N[3], Ataee H[3], Mehrvarz S[3], Hajighasemi F[3], Parniani M[1], Hoseinpour P[1,3,6], Aghaee P[3], Tayyebi M[1], Abbasi H[1], Abbasvandi N[7], Dadgari S[1], Shojaeian F[2], Hashemi MO[2], Akbari A[2], Akbari ME[2]* and Abdolahad M[3,4,8*#]

[1]*Department of ATMP, Breast Cancer Research Center, Motamed Cancer Institute, ACECR, Iran*

[2]*Cancer Research Center, Shahid Beheshti University of Medical Sciences, Iran*

[3]*Nano Bio Electronic Devices Lab, Cancer Electronics Research Group, School of Electrical and Computer Engineering, College of Engineering, University of Tehran, Iran*

[4]*UT&TUMS Cancer Electronics Research Center, Iran*

[5]*Laser and Plasma Research Institute, Shahid Beheshti University, Iran*

[6]*SEPAS Pathology Lab, Iran*

[7]*Department of Physics and Astronomy, University of Waterloo, Canada*

[8]*Cancer Institute, Imam Khomeini Hospital, Tehran University of Medical Sciences, Iran*

[#]*These authors contributed equally to this work*

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****Correspondence:***

Mohammad Abdolahad, Nano Bio Electronic Devices Lab, Cancer Electronics Research Group, School of Electrical and Computer Engineering, College of Engineering, University of Tehran, P.O. Box: 14395/515, Tehran, Iran, Tel: 0098(21)61114307/0098(21)88028367; Fax: 0098(21)888013201

Mohammad Esmaeel Akbari, Cancer Research Center, Shahid Beheshti University of Medical Sciences, P.O. BOX: 15179/64311, Tehran, Iran, Tel: 0098(21)22748001-2; Fax: 0098(21)22724090

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Abstract

Aim: Electrochemical Therapy (EChT) is a well-known low-side effect method for destroying inoperable superficial solid tumors. However, incomplete remission is one of its main limitations in clinical usage. In the present study, we administrated EChT guided by impedance spectroscopy in either non-operable or chemo/radioresistant breast cancer patients.

Methods: We previously introduced this method in mouse models. This paper conducted a pilot and non-randomized clinical study on 16 women with inoperable and resistant breast cancer tumors to conventional methods (chemo/radiotherapy) from March 2020 to July 2021. To improve the pathological response of EChT, we applied real-time impedance recording by probing the whole treated tumor and finding non-destructed lesions. EChT would treat those tumoral lesions immediately after detection.

Observations: Using EChT in non-operable breast cancer converts them to an operable state. In addition, real-time impedance recording during EChT helped us find more than 30 locations of remaining tumors that were approved based on a biopsy. This new approach of impedance-guided EChT may help physicians apply electrochemical tumor destruction more precisely with lower amounts of transmitted electrical charges.

Conclusion: This method showed an average treatment efficiency of 80.5 ± 18.7, with the lowest and highest values of 45 and 100%, respectively. After treatment, the average tumor size has significantly decreased, with a p-value of 0.003, indicating a strong positive response to the treatment. So, this method may shed new light on administrating EChT as a helpful complementary method for treating solid tumors.

Keywords: Electrochemical; Electrolysis; Electroosmosis; Pathological complete responses; Treatment efficacy

Introduction

Electrochemical therapy is a substitute approach for tumor therapy based on flowing weak, safe, and direct electric current to the cancer tissue through at least two noble or iron derivative

metallic electrodes located in the center and margin of a malignant mass. Previous reports declared that this method had shown significant efficacy *via* rapid local necrosis and low side effects [1-3]. Based on the evidence, EChT can activate many intracellular and extracellular mechanisms, which causes cancer cell death. Some of these mechanisms include induction of electrolysis, electroosmosis, ionic transmembrane flow, electroporation in tumoral tissues, and stimulation of the immune system [4-5]. However, this modality's fundamental mechanism of action in tumor destruction has not been well understood.

From 1978 when Nordenström first reported the clinical use of EChT in human tumors [6], many trials were released worldwide on its utility in treating and controlling non-operable and chemoresistant tumors, including breast, lung, thyroid, melanoma, liver, prostate, metastatic lesions and chest wall tumors [3,7]. Based on the evidence, the response rate in EChT was between 47% to 100% in superficial tumors [3,8,9]. A retrospective study that included 14 patients with Kaposi sarcoma revealed that the administration of EChT in these patients accompanied a 93% Pathologic Complete Response (PCR) rate [10]. Furthermore, in a study by Wu et al. EChT, was found to be a safe and effective procedure in treating unresectable carcinoma of the body and tail of the pancreas [11]. Similar results were reported in the treatment of hepatocellular cancer and liver metastasis in some other studies [12-14]. Notably, EChT can be used to treat benign tumors such as lingual hemangioma or benign prostatic hyperplasia [15-16].

Although the administration of EChT in tumor treatment is well-tolerated, obtaining PCR is under debate, and no standard guideline was reported for EChT [4]. Besides, we had previously introduced a new electrical probe that can detect the presence of cancerous lesions in the tissue, which was named Tumor Diagnostic Probe (TDP) [17,18]. TDP (Tumor Detection Probe) is an impedance-based device that was histopathologically calibrated to characterize different types of solid breast masses and can improve the accuracy of BI-RADS (Breast Imaging Reporting and Data System) scoring [17,18] especially in high-risk or borderline breast masses. It can characterize breast tumors based on their dielectric properties. It has two impedimetric parameters of Z1kHz (impedance magnitude in 1 kHz) and IPS (Impedance Phase Slope in the range of 100 kHz to 500 kHz) to diagnose the pathophysiological state of the tumor [17,18]. The sensitivity, specificity, and accuracy of TDP have been reported at 95%, 89%, and 93% in previous literature [17]. In the current study, a similar technology called Electrochemical Impedance Spectroscopy (EIS) was employed to improve the accuracy of tumor sampling and pathological diagnosis, as well as to aid in the early detection of high-risk lesions. It used pathologically calibrated impedance measurements by the same-treated platinum electrodes to find remaining non-treated lesions in the tumor bed; it has already been shown that it can assist in achieving PCR in animal models [19]. Impedance recordings were applied before and during EChT sessions to trace tumoral regions. This pilot study presents a unique opportunity to assess the potential advantages of integrating EChT treatment with concurrent monitoring using the same electrodes, leveraging impedance measurements.

Methods

Population

The trial designation was part of a registered trial in IRCT (trial registration ID: IRCT20190904044697N5). Twenty patients with breast cancer were registered, and sixteen were assigned for the study. Among them, nine patients had progressed tumor size under neoadjuvant chemotherapy, four were medically unfit for surgery (due to impaired cardiac function), and three patients refused any conventional therapy, including surgery and chemotherapy. They were recruited from two cancer centers from March 2020 to July 2021. Once patients were briefed about the procedure along with its advantages and drawbacks, consent was obtained (Figure 1).

The procedure of EChT

The patients underwent the EChT course between 2 to 7 sessions, and 9 out of 16 patients underwent surgery at the end of the study (ID numbers: 1, 5,7,9,11-15). Patients were sedated through local or general anesthesia based on their cardio-pulmonary function during the procedure. Then, the surgeon entered the integrated EChT needles from the skin into the depth of the tumor in a configuration in which needle electrodes covered a maximum of 3 cm of tumor in each course of therapy.

The voltages between anodes and cathodes in each needle were increased to about 10v, and the low current range was between 70 mA to 90 mA. After 15 min of treatment, the impedance of each smart needle was recorded, and the therapy was continued for further 15 min in other lesions. After termination of the treatment, the needle was removed from the breast. Patients were discharged under the supervision of an expert anesthesiologist in approximately 2 h to 3 h after final sedation medication administration if no medical problem occurred. Anode electrode that acidifies its peripheral ambient would be dehydrated during the therapy [20]. This would stop the ionic current flow between anode and cathode due to the lack of carrier solution. The alkaline saline was injected into the anode region after each 15 min of therapy to solve this problem. Also, the electrodes were connected to each other after 30 min to prepare a similar potential ambient and flow back some of the water molecules to the anode region [2].

After one week, we remeasured the tumor's impedance by smart needle and repeated the therapy in the remaining positively scored lesions with the same recording electrodes. If all of the lesions were negative for malignancy based on the impedance calibration, then we carried out a sonography-based biopsy for pathological evaluation of the EChT efficacy as well as the validity of impedance results.

The position and number of applied electrodes and the accurate guidance of electrodes to the proper tumoral lesion are crucial for the best pathological responses. To achieve such optimizations, we entered the electrodes from the longest side of the tumor, matched the impedance scores with imaging evaluations (especially intra-therapeutical sonography), and changed the position of the electrodes after each 30 min to expose the whole tumor volume for EChT. Through the next therapy session, treated lesions were evaluated by impedance scoring, sonography, and in some cases, biopsy. Biopsy was employed when impedance recording findings and imaging assessments on the same lesions were discordant. In this situation, a frozen section from the biopsied specimen was the main indication to show treatment.

Endpoints of study and follow-up

Patients' tumor response was evaluated through physical examination and sonography; if these were not conclusive, MRI was performed. Evaluation through physical examination and imaging modalities was done before beginning of each EChT course session,

Table 1: Demographic variables and basic characteristics of patients, and overall study outcome of 16 patients investigated in this study. The patients' ages ranged from 33 to 79 years, with an average age of 51.7 ± 14.4 years. The ki67 values varied from 8 to 45%, with an average of 27.3 ± 9.3%. The tumor sizes for T1, T2, and T3 groups were 1 (6.2%), 10 (62.5%), and 15 (31.3%), respectively. The treating electrical power ranged from 396 to 1141 mW, with an average of 191.7 ± 785.2 volts. The treatment time varied from 100 min to 483 min, with an average of 266.8 ± 118.2 min. The mentioned method showed an average efficiency of 80.5 ± 18.7, with the lowest and highest values of 45 and 100%, respectively. The average percentage of changes and reduction in size was 57.9 ± 25.9%, and the difference in average tumor size before and after treatment was statistically significant (p=0.003).

Variable	Mean ± SD / n (%)
Age (year)	51.7 ± 14.4
Ki67 (%)	27.3 ± 9.3
Tumor histology	
IDC	15 (93.8)
ILC	1 (6.2)
Tumor Size	
T1	1 (6.2)
T2	10 (62.5)
T3	5 (31.3)
TNM Staging	
N0	9 (56.3)
N1	3 (18.8)
N2	4 (25.0)
Electrical Power (mW)	785.2 ± 191.7
Total Treatment Time (mints)	266.8 ± 118.2
Number of sessions (n)	4.0 ± 1.4
Treatment Efficiency (%)	80.5 ± 18.7
Difference in tumor size (%)	57.9 ± 25.9
Required charges (A.S)*	17.1 ± 11.0
Transmitted charges (A.S)**	1057.4 ± 729.1

*Required charges to induce 1% necrosis in the tumor (A.S)
** Total efficient transmitted electrical charges (A.S**)

first week, first month, and three months after the complement of EChT. In each session of therapy, EIS was used to find the tumor remnant before starting tumor destruction by EChT. When real-time EIS results conflicted with radiological and clinical tumor assessments, we conducted biopsies on the lesions, followed by a comparison of the outcomes with EIS scores. Finally, patients underwent a biopsy one month after completion of EChT. Nine patients who were eligible for surgery underwent surgical resection and permanent pathology on the treated tumor was investigated accordingly. Adverse effects were assessed throughout and after the EChT sessions within the specified time intervals.

Working mechanism of EChT mediated impedance recording

Each single needle EChT electrode has an integrated nanoporous Pt-Ir (9:1) anode (thickness of 250 μm) with tunable size and a peripheral venous catheter (gauge 14) as cathode with the capability of recording the therapy efficacy using an Intra-therapeutic impedance analyzer by the same electrode. An integrated impedance recorder board was matched with the EChT electrical stimulator and showed the state of tumor destruction during the procedure. Both wet (chemically etching with Aqua Regia solution) and dry etching (physically etching with fluoride-based gas) were used for platinum etching. The Pt needle was placed in Aqua Regia (8:1 mixture of HCl and HNO_3) for wet etching on a hotplate at around 60°C for 180 sec [21-23]. For dry etching, the optimized experimented parameters were applied to achieve the uniform porous platinum electrode with reactive ion etching (RIE) (SensIran company) (RF power = 250 W, gas processing mixture = SF_6 (150 sccm) + O_2 (150 sccm), etch time = 20 min, and gas pressure = 20 mTorr) [24].

For impedance recording, the Electrochemical Impedance Spectroscopy (EIS) technique was used for measuring electrical impedance magnitude |Z| and phase (degree) as a function of frequency to characterize the biological nature of the tissue [25]. In this study, the same EChT electrode used for treatment by connecting to the impedance analyzer system is used to measure impedance. By scanning frequency from 1 Hz to 1 MHz, we observe frequency responses from interactions of electrode and breast tissues. The slope of the impedance phase diagram in the frequency ranges of 100 kHz to 500 kHz (called IPS: impedance phase slope in the frequency ranges of 100–500 kHz) is the most crucial parameter in recognizing tissues by needle electrodes. The normal and necrosis-induced EChT treatment breast tissues show a positive IPS, while cancerous and non-treated tissue shows a sharp negative IPS. The schematic setup for EChT treatment during this study is presented in Figure 2.

Observations and Results

Pathologic and radiologic response

Sixteen patients with locoregional breast cancer were recruited for 16 months in this study. Table 1 shows patients' characteristics and clinicopathological features. All 16 patients with 24 breast lesions in this study responded to EChT. Thirteen of twenty-four (54%) lesions showed more than 80% tumor necrosis, and 7 (29%) achieved PCR. It is observable that impedance-guided EChT helped us in inducing 30% to 100% tumor necrosis with total transferred charges of about 396 to 1141 (785.2 ± 191.7) Amp.Sec, respectively. Treatment efficiency (EChT induced tumor necrosis) and the total efficient transferred electrical charges in each tumor were described in Figure 3 and supplementary Table 1. Nine patients underwent surgical resection, and none experienced local relapse after three months.

Real-time monitoring of EChT with EIS

To ensure EChT treatment efficacy and to prevent over-treatment, EIS was used before starting each treatment session. The comparative results between impedance recording and pathological diagnoses as a gold standard were presented in supplementary Table 2.

Two hundred and eight EIS measurements were performed during this cohort, and 33 biopsies were carried out in the case of discordance between the result of EIS and imaging modalities. Based on the biopsy, which was occasionally performed prior to each session of EChT, real-time impedance scoring showed exact matching with the necrotic or viable state of the tumors. New calibration cut-offs (1800Ω for Z1kHz and 1.5 for IPS) resulted in 88% sensitivity, 100% specificity, and 90.9% accuracy. AUC (=0.94, P-value <0.001) shows a significant relation between EIS and the pathological responses of the treated lesions (Figure 4a, 4b). In some cases, a great match was observed between the scores and diagnoses, which were more precise than radiological imaging. The crucial role of intra-therapeutical impedance recording was clarified in some patients (e.g., patient ID 11) whose MRI declared the absence of a vital tumor, while the scoring result of real-time impedance measurement from the same

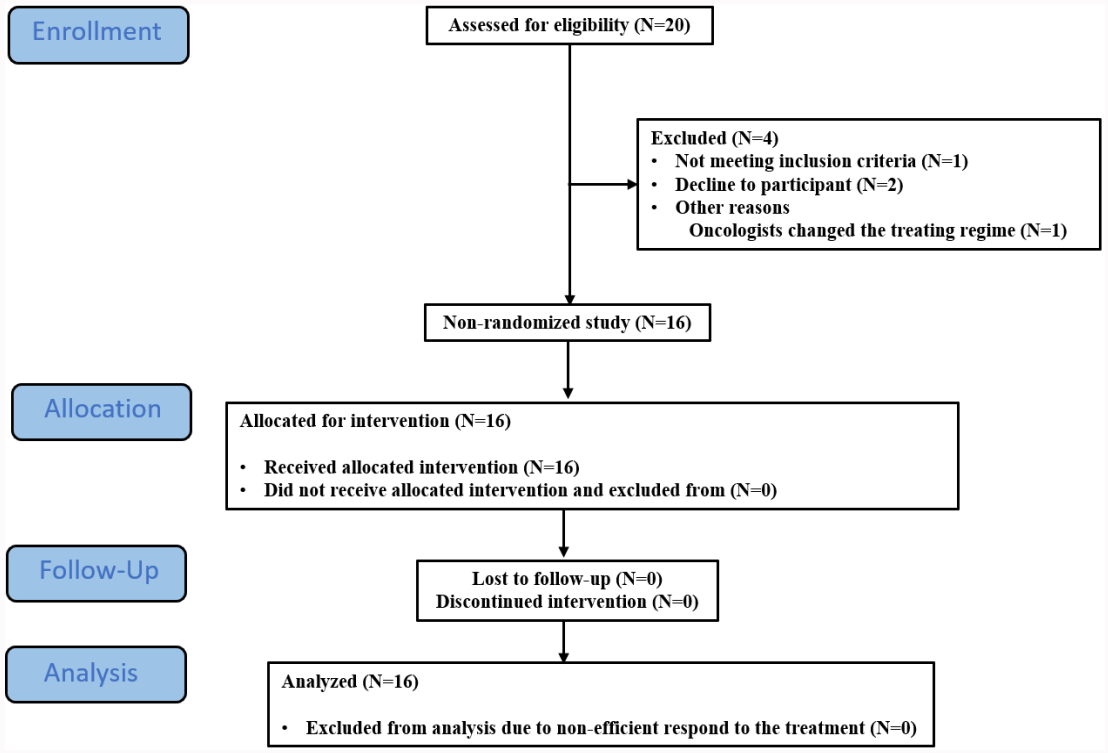

Figure 1: TREND diagram for electrochemical treatment evaluations in the efficacy analysis.

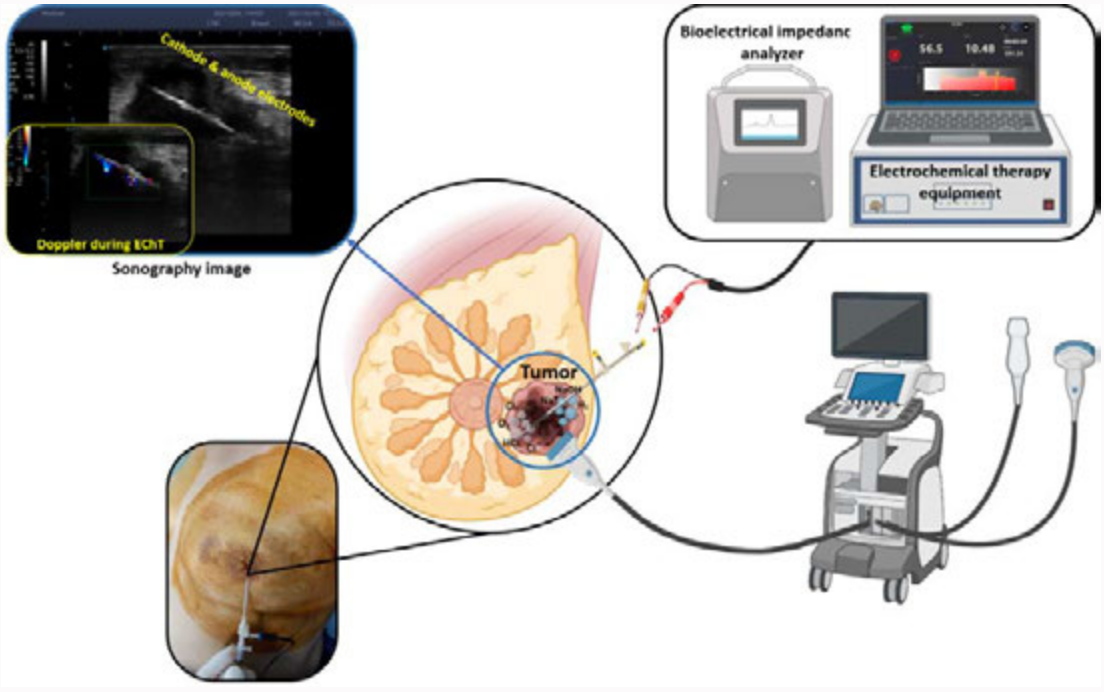

Figure 2: The schematic of the EChT treatment procedure with intra-operative impedance recording. Before starting the treatment in the next sessions, each lesion was recorded by impedance spectroscopy, and positively scored lesions were re-treated.

lesion was in contrast. Interestingly, the biopsy of the mentioned lesions confirmed the correct scoring of the Impedance results (e.g., Patient ID 11: Viable tumoral cell: 30% and necrotic area: 70%) (Figure 4c). Hence, real-time impedance recording prevents missing the remaining vital tumors and helps reduce the overtreatment by EChT in a necrotic lesion (Figure 4d).

EChT adverse effects

Side effects of treatment by EChT include pain, fatigue, and fever which are presented in Figure 5. The pain level was quantitatively scored due to their statements (pain levels: 0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain). Most declared moderate to severe pain immediately after EChT and were controlled by painkillers.

a)

Cancer type	Tumor lesion	CR		PR		NC		PD		CR+PR	
		N	%	N	%	N	%	N	%	N	%
Breast cancer (IDC)	23	7	30	16	70	0	0	0	0	23	100
Breast cancer (ILC)	1	0	0	1	100	0	0	0	0	1	100
Total	24	7	30	19	85	0	0	0	0	24	100

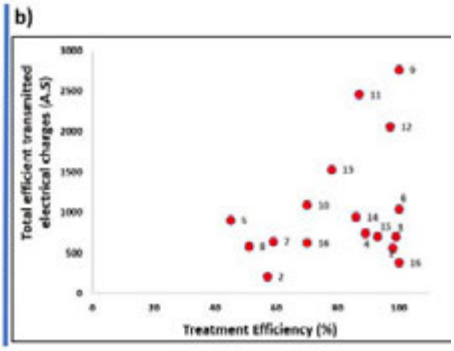

Figure 3: a) Objective remissions in 16 cases of cancer tumors treated with EChT. Responses were evaluated with MRI, ultrasonography, or permanent pathology. CR: Complete Response; PR: Partial Response; NC: No Change; PD: Progressive Disease
b) Treatment efficiency (EChT induced tumor necrosis) and the total efficient electrical charge in each tumor diagram. Our gold standard for efficiency was a pathological evaluation of biopsied samples from the tumor.

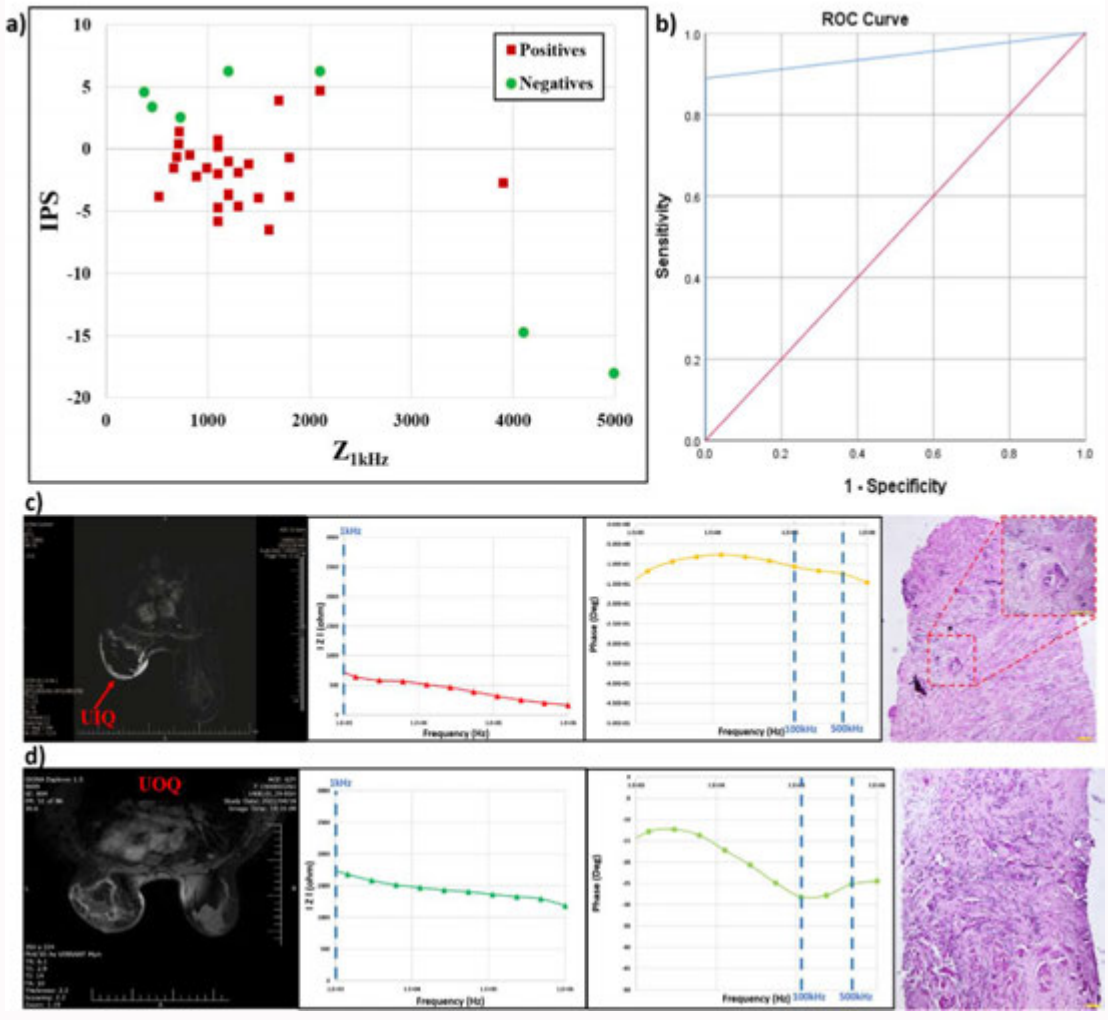

Figure 4: a) IPS-Z1kHz diagram of treated lesions (N=33) were evaluated by impedance scoring, b) ROC curve. The MRI image and impedance diagram (Impedance magnitude and phase) of c) positively and d) negatively diagnosed impedance lesions, and c) biopsy slide of those lesions was stained using Hematoxylin and Eosin (H&E). Each scale bar is equal to 100 µm.

Skin burning resulting from the release of treatment byproducts, such as HCL and NaOH, emerges as a notable concern within EChT, particularly for superficial breast tumors, which had not been discussed in the literature yet. This burning would be occurred around the electrodes, even if they were electrically insulated, due to acidosis and alkalosis of the anode and cathode, respectively. The non-buffer pH solution would diffuse to the skin through the media made by needle entrance from the surface. To reduce this side effect, we washed the entrance of electrodes on the skin with a physiological serum to balance the surrounding tissue's pH. Moreover, silver sulfadiazine

Item	Mean±SD / n (%)
Pain (Yes)	12 (75.0)
Fatigue (Yes)	2 (12.4)
Fever (Yes)	1 (6.2)

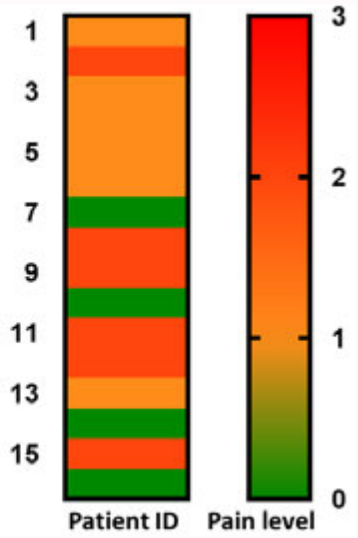

Figure 5: EChT treatment side effects on 16 patients registered in this study (pain levels: 0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain).

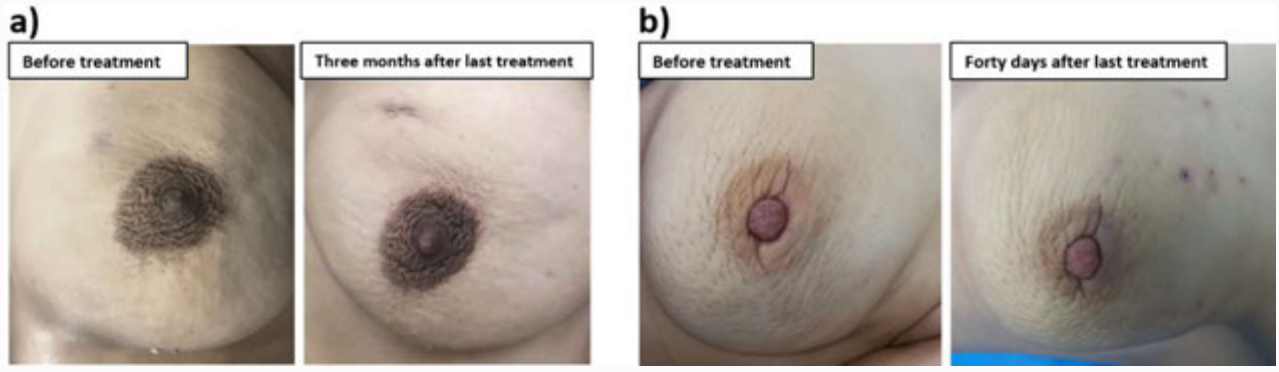

Figure 6: Healed wound in treated location on skin based on the mentioned procedure in patient ID a) 6, and b) 7.

and carbonate calcium creams were rubbed on acidified and basified regions after each therapy session, respectively. Zinc oxide was also rubbed on both regions one day after. Figure 6 revealed the healed burned locations on the skin based on this treatment procedure.

Discussion

Electrochemical Therapy (EChT) has been widely studied since its proposal by Nordenström in 1978 [6], as a potential treatment for malignant tumors. Many of these studies were conducted on animals [26,27], and some of them were performed on human tumors such as skin cancers, hepatic lesions, pancreatic lesions, lung cancer, and even benign tumors [3]. Nevertheless, most clinical usages of EChT were in advanced cases that had not benefited from conventional therapies. In addition, these studies belong to the 20th century, and the administration of EChT has become limited in the last 20 years due to a lack of achieving PCR [4]. Therefore, finding a solution to achieve PCR can assist this invention being administrated in treating locoregional tumors.

Up to our knowledge, there is a limited report of EChT in breast cancer in an animal model [27]. Traditionally, imaging modalities were applied to investigate the response to EChT. Although MRI is a well-established method in predicting the pathological response, it showed discrepancies with pathological results, possibly due to its inability to distinguish between inflammation and cancer-based dynamic enhancements [28]. Hence, the present study is the first trial that used the impedance-guided modified EChT method to destroy the non-operable breast tumors with optimized transferred electric charges and low side effects. Sixteen barest cancer patients with 24 lesions were recruited in the present study. The study's findings are promising - with an average treatment efficiency of 80.5 ± 18.7 and a strong positive response to the treatment, indicated by a significant reduction in tumor size (p-value of 0.003). The range of results varied, with the lowest value being 45% and the highest being 100%. This method has the potential to be a valuable complementary treatment option for solid tumors. Real-time EIS assisted in finding remnant tumors in patients before stating EChT, and there was a significant correlation between EIS reports and pathological response. A fundamental role of real-time EIS in archiving PCR was shown in the cases where MRI had discrepancies with EIS results.

On the other hand, side effects of EChT treatment in patients, such as pain (75%), fatigue (12.4%), and fever (6.2%), were reported in this series. These side effects can limit the administration of EChT in breast cancer; However, all of them were alleviated by painkillers and antifebriles. As Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) suppresses the immune system and immune response in the microenvironment of tumors [29,30], patients use other painkillers rather than NSAIDs.

After a six-month follow-up, it was found that none of the

nine patients who underwent surgery experienced a local relapse. However, since this study was conducted on a limited population, further research is necessary to confirm the effectiveness of modified EChT as a complementary treatment protocol for breast tumors. These findings provide new insights into the use of modified EChT as a helpful complementary method for treating breast tumors.

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