# *Neoadjuvant electrochemotherapy of breast cancer: our experience on first case treated in Italy*

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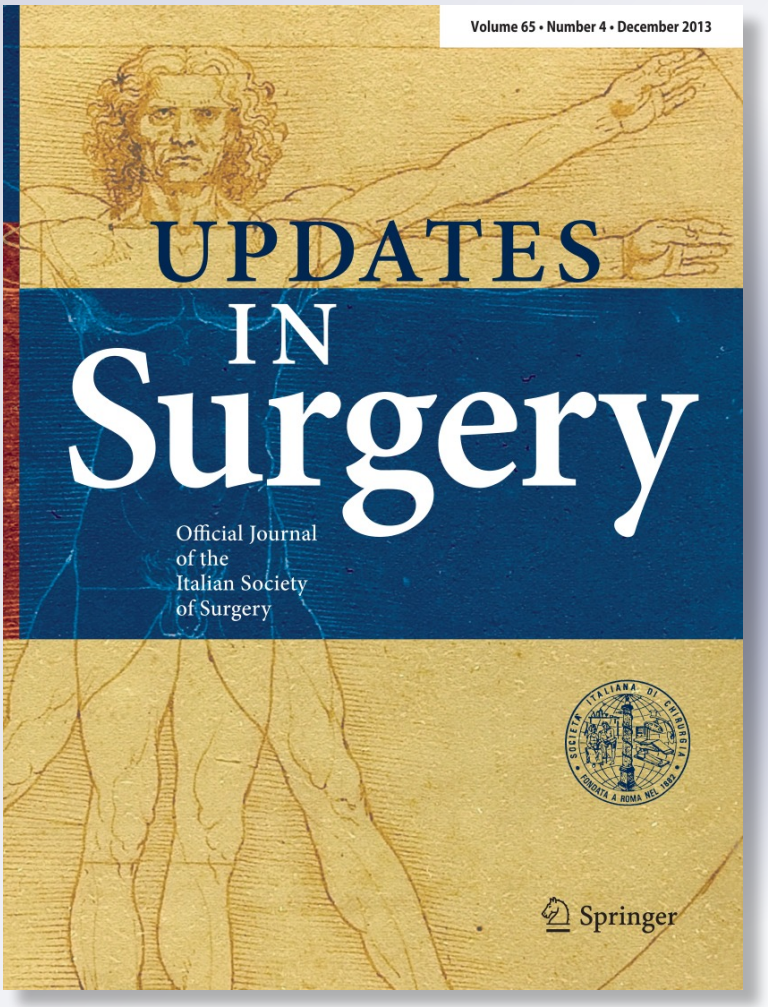


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CASE REPORT

# Neoadjuvant electrochemotherapy of breast cancer: our experience on first case treated in Italy

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## Introduction

Experimental studies on guinea pigs and humans have shown that the electric pulses allow the opening of suitable pores which increase the drug's intracellular access.

Chemotherapy absorption following electroporation is better than intravenous drug administration. Until now electrochemotherapy has been used as a palliative remedy in cases of subcutaneous recurrences of melanoma and mammary carcinoma. This is the first case in Italy of primary mammary tumour treated by electrochemotherapy.

## Case report

In 2008, the patient P.A., 68 years old, presented an infiltrating lobular carcinoma on the left breast with extensive cutaneous involvement, presence of vasal embolism, G2pT4pN1 3LN+; RE 85 %, RPg absent, Ki 1 %, Her+−. Vertebral bone metastasis was present. She was treated with chemotherapy with poor response on the breast and secondary locations. A year later, we examined the patient. An objective examination revealed a voluminous neoplasia of the left breast set on a deep plane and involving the skin above the gland, extending up to 1 cm from the lower margin of the left collar bone and 2 cm below the homolateral submammary groove. Despite the large volume of the disease, it was however stable and not in progression. The general conditions of the patient were good. Performing a radical mastectomy posed important problems of risks of a relapse in surgical margins even after extensive demolition and reconstruction with flaps. In preoperative preparation, the patient underwent mammography, mammary scintigraphy MIBI TC99 and mammary RMN (Figs. 1, 2).

On the 4th June 2009, with the informed consent of the patient and the Ethical Committee's approval, the patient underwent electrochemotherapy treatment (electroporation and preliminary administration of 27 mg intravenous Bleomycin). One hour before being given the bleomycin, the patient was pre-treated with an intravenous infusion of betamethasone 4 mg and a 10 mg intramuscular injection of chlorpheniramine maleate. The patient was under general anaesthesia. Bleomycin in the dose of 27 mg in 250 cc of physiological solution was administered rapidly and after 8 min and not later than 25 min from the end of drug administration, the electrode was used connected to the Cliniporator generator. Multiple electrodes were carried out in the entire area macroscopically involved by the neoplasia, particularly on the margins. The inserts were made overlapping the margins to avoid leaving undertreated or untreated areas. Each electrical current pulse lasted 1 ms. The amount of electrical current generated was recorded in the special report system which comes with the Cliniporator. In the case of inadequate needle implants or poor pulse tissue response, indicated by the generator, further implants with microneedles and electric pulse administration were carried out. The treatment lasted 25 min. At the conclusion of the session, the skin was abundantly hyperemic and showed the signs of the multiple inserts of the needles. The bleeding that occurred was very modest and resolved by hemostasis using moderate compression. In the following days the patient was medicated,

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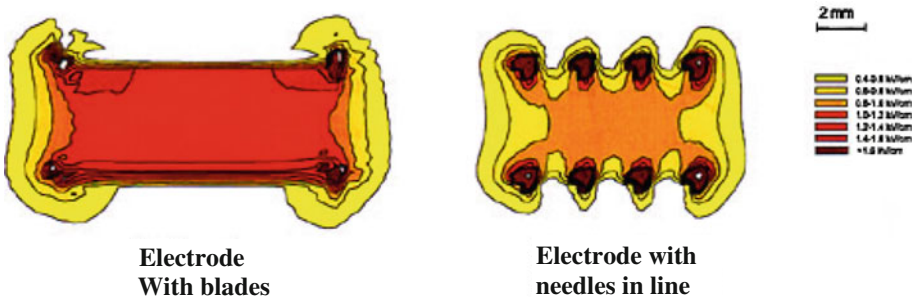


**Fig. 1** Electric field distribution. Contrary to other methods of local treatment, it is possible to calculate the exact characteristics and dimensions of the electric field. This permits us to exceed the typical limits imposed by other technologies utilizing heat or cold represented by the difficult identification of treatment margins. With electrochemotherapy, one has the certainty of having involved the entire tumoral lesion in the treatment

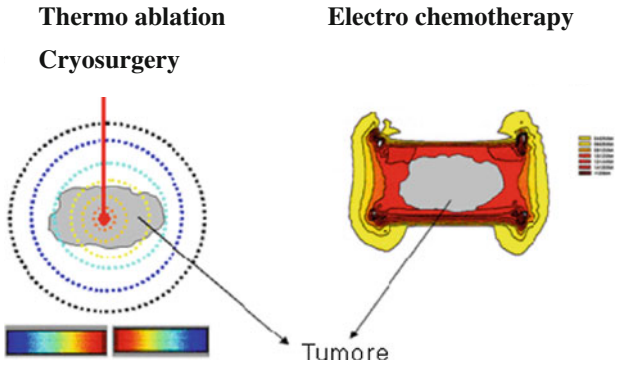


**Fig. 2** Safety margins. The most important advantage of electrochemotherapy, compared to other treatments, is the treatment focusing. As shown in the diagram with the ability of an exact modeling of the generated electric field, it is possible to cover the entire tumoral zone to be treated, something which does not occur in thermo ablation and cryosurgery

small scabs in the insert points were formed which detached themselves spontaneously in 10 days without leaving any signs. The skin appeared hyper chromatic for 20 days, then in 30 days gradually returned to normal skin colour. In the days that followed the treatment, the patient was checked for hemochrome, hepatic and renal functions which were always satisfactory. Objectively, a clinical reduction of the volume of the neoplasia was recorded and approximately 1 month after electrochemotherapy, on the 8th July 2009, the patient underwent a radical mastectomy with large cutaneous excision. The extemporary histological examination of the margins showed clear margins and the absence of neoplasia.

The neoplasia showed partial infiltration in the underlying pectoral muscle and therefore, during the mastectomy, intra-operation electrochemotherapy was carried out on the areas of risk. The skin replacement was obtained by fitting a large flap of thoraco-epigastrical cutaneous bundle of medial peduncle. An axillary drainage and two aspiration drainages of Redon were positioned to protect the transposed flap. The drainages were removed after about 7 days when the post-operational seroma diminished to 40 cc daily. The final histological examination showed remarkable reduction of the neoplasia mass and confirmed negativeness of the surgical margins and of chest wall obtained with the first treatment of electrochemotherapy. Out of 25 lymph nodes removed, three were found to be positive. One month after surgical procedure, the patient underwent chemotherapy. The patient refused to undergo chemotherapy and radiotherapy of the mammary region and up till now, after 30 months of thorough follow-up, has not shown signs of local relapse.

## Discussion

At the time of the evaluation on the first year after the diagnosis, the patient refused further chemotherapy. Furthermore, a radical surgery was not allowed because of the tumour extension and infiltration on the chest wall.

This clinical context suggested an attempt at cytoreduction with a method that until now had place only as a palliation in secondary cutaneous and subcutaneous locations.

The above-mentioned clinical case was particulary interesting because despite chemotherapy, the patient was inoperable for neoplastic infiltration of the chest wall. So the first electrochemotherapy session led to a mass of cytoreduction while the intraoperative local electrochemotherapy treatment made possible to succeed in the complete reclamation of the coastal wall in a long-term survival, without any local recurrence to date, although patient refused postoperative radiation therapy as well as additional chemotherapy.

Electrochemotherapy (ECT) is a method of local treatment for solid cutaneous and subcutaneous tumours based on the electroporation of the tissue. ECT originated and was developed on an idea of Dr. L. M. Mir (Institute

Gustave Roussy, Villejuif, France) by applying electroporation together with the administration of low doses of anti-tumoral drugs: the electric pulses make the cellular membrane more permeable, significantly increasing the intracellular concentration.

The first clinical experimentation for the treatment of cutaneous and sub-cutaneous tumours with electro-chemotherapy was carried out in the early 1990s. The first positive results were subsequently confirmed by other clinical trials. The European Community financed and promoted a large clinical study with the aim of defining the "Standard Operational Procedures for Electro-Chemotherapy in Europe" (ESOPE V FP Quality of Life and Management of Living Resources Programme 2003–2005). The results of the ESOPE project allowed the precise definition of the indications and modalities of electrochemotherapy in clinical practices, confirming that the electrochemotherapy is a simple, effective and safe procedure. A positive response has been obtained in 85 % of the treated nodules (73.7 % of complete response). The study was managed at four important European oncological institutes: Cork Cancer Research Center, Cork (Ireland), University Herlev Hospital, Copenhagen (Denmark), Institute Gustave Roussy, Villejuif (France), Institute of Oncology, Ljubljana (Slovenia) [1, 2].

Subsequently, the publication of the results of the ESOPE study in the European Journal of Cancer, several clinical studies were published at the end of 2006, confirming the level of effectiveness, repeatability, safety and tolerability of the electrochemotherapy [3–5]. The purpose was purely palliative. The candidates were not susceptible to surgical treatment or responded little to chemotherapy or radiotherapy. Until today, before the case in discussion, electrochemotherapy on primitive mammary neoplasis has been carried out on just 20 women in Europe. The case illustrated represents the first and up till now the only treatment performed in Italy on primitive mammary neoplasis and not on its metastasis. In the electrochemotherapy experiences, both bleomycin and cisplatin were utilized. In vitro the cytotoxicity of the bleomycin and the cisplatin is increased from 1.000 to 10.000 times when the cultures undergo electroporation.

As it is less toxic, bleomycin was found to be the most effective drug in topical treatment of the neoplasis. The side effects of the bleomycin are represented by the possible, although rare, onset of allergies, therefore, 1 h before the treatment, we have done the pre-medication with corticosteroid and anti-histaminic drugs. The toxicity of the drug appears at the medullar level with a deficiency of the hemopoiesis, hepatic and renal toxicity, so the patient have to be monitored during the following 20 days.

For best results, the drug must be administered rapidly and the electroporation must begin within 8 min of the complete administration of the drug and to be completed in 25 min.

## Conclusions

Electrochemotherapy combines two effects: the administration of reduced drug doses and electroporation of the cell membranes with electric pulses. Electroporation allows drugs to penetrate the tumoral cells more easily thereby increasing the anti-tumoral effectiveness, enabling drugs which do not or insufficiently permeate the cell membrane, to perform locally and at low dosages against their intrinsic cytotoxicity. The electrical pulses are applied directly to the tumoral area and this makes electrochemotherapy a targeting and localized treatment. In fact, the drug goes through the cells in the zone of electric pulse application and shows its efficacy. Electrochemotherapy has numerous advantages such minimizing the side effects on the patient, the possibility of being repeated, the capability to preserve organ functions and surrounding healthy tissue. It has also the important advantage of being well-tolerated by the patient, therefore, allowing an immediate recovery (Figs. 1, 2).

Studies in literature have demonstrated that electrochemotherapy is indicated for some types of primitive cutaneous tumours such as basocellular and spinocellular carcinoma, in single and in transit melanoma metastasis and in cutaneous metastasis of other tumours independently from their histology.

In these last two cases, the treatment, although just palliative, is able to significantly improve the quality of the patients' life.

Additionally, electrochemotherapy may be utilized as an adjuvant analgesic and hemostatic treatment.

The good results achieved in this case encourage us, with the Ethical Committee's approval, to set up controlled clinical trials to study the effectiveness of electrochemotherapy as a neo-ancillary treatment for breast cancer compared to the current well-established results in neo-ancillary classic chemotherapy and in the sterilisation of the margins, after conservative mammary surgery with the aim of reducing the risks of local recurrence.

In addition to the above illustrated case, neoadjuvant chemotherapy brings about the same results in terms of cytoreduction and recurrence rate, but not significant yet for their assessment in the still short observation period.

**Conflict of interest** None.

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