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# ELECTROCHEMOTHERAPY: A novel treatment option for unresectable tumors.

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## ABSTRACT

Electrochemotherapy (ECT) is a combined treatment that exploits the administration of chemotherapeutic drugs and cell membrane reversible electroporation. ECT increases elective drug penetration into cytoplasma of treated tissues and allows a tissue sparing treatment. This article describes a single center experience of ECT for the treatment of unresectable cutaneous and subcutaneous tumors. Safety, tolerability and correlation between tumor's characteristics and clinical response were the question of research. On the basis of the study, other important application should start.

Keywords: electrochemotherapy, surgical oncology, melanoma, skin tumor

## BACKGROUND

Technology has powerfully entered in all surgical field, in the treatment of functional diseases (Stabilini 2013), of inflammatory diseases (Fornaro 2008, 2009), and in cancer treatment. The present study is related to an application of technology in oncological surgery.

Electrochemotherapy (ECT) is a combined treatment that exploits the administration of chemotherapeutic drugs and cell membrane reversible electroporation. Electroporation, induced by specific electrodes, increases elective drug penetration into cytoplasma of treated tissues, up to 1000 folds than the traditional way of administration. This allows the administration of low dose of chemotherapeutic drug, with consequent less rate of collateral effects. Treatment is "tissue sparing" because just pathological cells in rapid turn-over die for apoptosis due to DNA damage. Instead, surrounding stroma and healthy cells are not affected by the treatment (selective cytotoxicity) (Cadossi 2014).

First phase II clinical trials belong to the nineties (Belehradek 1993), but the entrance of this treatment in clinical practice is quite new. Major evidences for ECT are on plurirecidive or extensive epitheliomas and other Non-Melanoma Skin Cancer (NMSC) (Rotunno 2016); in transit (Quaglino 2008) or at distance (Kunte 2017) cutaneous and subcutaneous metastasis from melanoma; cutaneous metastasis from breast cancer (Campana 2012); cutaneous Kaposi sarcoma (Di Monta 2014). More recent studies are examining the effect of ECT in head and neck neoplasias, both cutaneous one, and mucosal one (Bertino 2016), vulvar relapses of disease (Perrone 2019), bone metastasis (Bianchi 2016), metastatic (Edhemovic 2014) and primitive (Tarantino 2017, 2018) hepatic tumors, locally advanced pancreatic cancer (Granata 2015).

In 2006 European Standard Operating Procedures of Electrochemotherapy (ESOPE) were published, giving the "rules" of correct treatment plan and clinical results. Objective clinical response (defined as the sum of complete and partial response) observed in that study was 80% (Mir 2006, Marty 2006).

Based on the rise of ECT treatment in Europe, from 2016 our Institute have started to use it in clinical practice. Key points of study were safety and tolerability, taking in great account the pain linked to the treatment, and clinical response related to tumor characteristics.

## MATHERIALS AND METHODS

From November 2016 to April 2019, 35 electrochemotherapy treatments with intravenous injection of bleomycin for unresectable primary or metastatic cutaneous neoplasias were performed. Inclusion criteria were pluricecidive or extensive epytelioma; in transit or at distance metastasis from melanoma; cutaneous metastasis from breast carcinoma; vulvar relapses of disease; cutaneous and subcutaneous metastasis from visceral neoplasms; painful bone metastasis. Exclusion criteria were a previous prolonged treatment with bleomycin; life expectancy lower than 3 months; patient refusal of proposed treatment. Indications and timing of treatment were multidisciplinary decided.

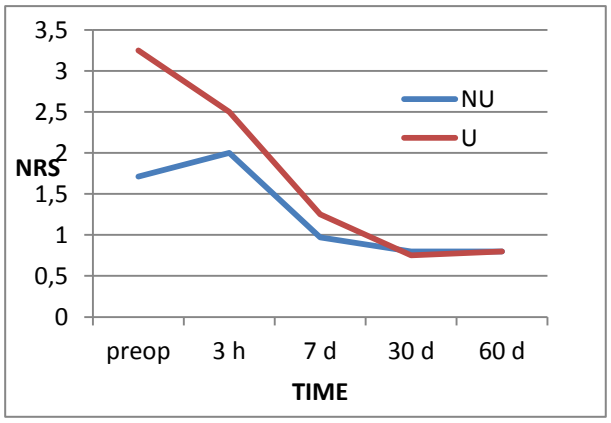
Every treatment was administered by one of 3 surgeons of a single center. In particular, one of the surgeons and Author of this article (M. M.) was in the operative room in every treatment and performed 33 treatments as first operator. Every patient was adequately informed about technical and clinical aspects of ECT. Informed consent for treatment and scientific research was achieved.

Bleomycin was administered intravenously at the dosage of 15.000 IU/m2. Dosage was adjusted according to glomerular filtration rate (GFR). We used Cliniporator VITAE$^{TM}$, that is CE certified for use on patients (Mir 2006), as the technological platform to deliver the pulses. Pulses were delivered through the use of multiple needle electrodes joined in a pre-set

geometry for skin or subcutaneous tissue lesions; or through individual needle electrodes in a custom modality for deep-seated tumors and bone. Pre-set geometry electrodes were needle row or hexagonal shape.
A prospectively maintained database was created in November 2016. Clinical features, treatment response and adverse effects were collected and evaluated for a minimum of one month follow-up. Every treatment was performed according to the European Standard Operating Procedures of Electrochemotherapy. Clinical results were evaluated according to RECIST (Response Evaluation Criteria in Solid Tumors) criteria (Therasse 2000).

**RESULTS**

Thirtyfive ECT treatments were performed in 26 patients. For practicality we chose to list the individual treatment instead of individual patient, because clinical presentation and personal features could vary through time.
Median age was 74.2 years, ranging from 34 to 103 years. In 25 cases ECOG (Eastern Cooperative Oncology Group) Performance Status (Oken 1982) was 0-1; in the remaining 10 cases ECOG was 2-3. ASA (American Society of Anesthesiology) score was greater than 2 in 19 cases. Primitive histotype was melanoma in 18 cases, breast in 7 cases, non-melanoma skin cancer (NMSC) in 6 cases. Remaining 4 treated were metastasis from rectal carcinoma or kidney and vulvar local relapse carcinoma. Tumors were classified according to histotype, maximum size and setting of tumor growth: nodular, flat, and ulcerated for cutaneous or subcutaneous lesions; deep for visceral or intra-abdominal lesions.
ECT was administered under general anesthesia in 21 treatments, under loco-regional anesthesia in 5 cases; in 10 cases just local anesthesia, with or without sedation, was adequate to perform the treatment. In two cases, electrodes were positioned under CT scan. Mean operative time was less than 5 minutes, from the first to the last pulse. In the greater part of cases, patient was discharged the day of treatment or in post-operative day (POD 1). Cardiac arrhythmia was registered as the only intraoperative complications, requiring electric cardioversion, without further sequelae.
All the patients completed the minimum one month follow-up. Minor later complications, such as fever and local ulceration, affected few patients and the introduction of steroid premedication drastically reduced the incidence. Arising pain compared to basal pain was observed in 2 cases. In 30 cases, patients did not take any pain medication at the POD 7 ambulatory control. Complete clinical response was achieved in 15 cases (43%), while partial clinical response in 16 cases (46%). Thus, objective response rate is up to 89%. Correlation between demographic and pathological data and clinical response are listed in appendix A. A visual representation of pain is reproduced in picture 1.




Picture 1: Trend of pain before and after ECT, evaluated according to NRS (Numerical Rating Scale)

Preop: preoperative NRS
3 h: NRS after 3 hours
7 d: NRS after 7 days
30 d: NRS after 30 days
60 d: NRS after 60 days
NU: not ulcerated tumor

**DISCUSSION**

ECT is a relatively new kind of treatment; it is not so diffused in Europe, but its knowledge and application fields are rapidly increasing.
ECT let patients be eligible for a treatment, regardless of comorbidities and ASA score, thanks to its short operative time and lack of major collateral effects. Biological age and life expectancy and, most of all what we expect from treatment (bridge to radical surgery; combination with systemic treatment; palliation for ulceration or pain), are the key features to look for during the first visit.
ECT is an alternative to surgery for unresectable tumors. The criteria of unresectability are very subjective and diversified. Extension of disease is the main contraindication to a radical resection, both for dimension, both for number of lesions, as we classically observe in patients affected by in transit melanoma. Otherwise, severe comorbidities with high operative risk could be the reason why some patients are not candidate to an elective radical surgical procedure. Most of patients are affected by great lesions that require an extensive and demolitive intervention: the length of necessary general anesthesia and the long post-operative course often worry the patient and the surgeons, too. On the contrary, ECT could be delivered under loco-regional anesthesia or under local anesthesia, with a mild sedation. Operative time is really short. According to ESOPE, 8 minutes after the drug is administered, the operator can deliver pulses for 20 minutes. Therefore, maximum operative time is less than 30 minutes. Short operative time and the possibility of non-general anesthesia are perhaps the reason why 13 patients over 80 years age old are included in our study. Old age must

not discourage, on the contrary ECT should be taken into account when lesion are not so big and devastating.
Aims of ECT treatment could be several. The first one could be palliation in case of painful or bleeding tumors, that is frequent in the case of in transit metastases from melanoma or bone metastases. In certain cases, ECT is a neoadjuvant treatment to a radical surgical, with the purpose to reduce tumor size and let a less invasive operation. In few and selected cases, treatment is administered with curative purpose, as an alternative to surgery. Treatment could be replicated in selected cases, such as a partial but convincing response or a relapse of disease in untreated area when first treatment produced a complete response.
When we analyzed database, it was evident that in the first 10 ECT treatments, number of pulses were bigger and total operative time longer than from the 11th case. On the contrary, after 10 treatments, operative time was shorter and local complications (such as local edema or ulceration) less frequent, with the same clinical results. For example, we observed that needle row electrodes are more adequate for the treatment of head and neck lesions, because they created less local inflammation, which is at the basis of local edema; clinical result were the equivalent to using the hexagonal electrode. This let us to say that learning curve is quite fast and the choice of the electrode is the key for a good outcome.
Rising experience of ECT, a premedication with one shot steroid, intravenously administered just before bleomycin, has proven to reduce the rate of predictable collateral effect drug-related, such as asthenia, fever and local edema. One shot steroid administration does not affect clinical response after ECT.
To answer our previous question about ECT, this treatment seems to be well tolerated by patients. No severe adverse event was observed in our series. Cardiac arrhythmia was registered in a patients with chemotherapy-induced cardiopathy, at the end of 20 minutes of pulses on chest cute; probably a mechanical stress due to muscle contraction contributed to its genesis.
Pain is universally considered the most important trouble by the side of patients. Picture 1 visually describes the trend of pain, measured using Numerical Rating Scale (NRS), stratified in ulcerated and not ulcerated tumors. Patients with ulcerated tumors are affected by a higher value of pain, at the baseline. After treatment a gradually descending trend is observed in both class of patients. In particular, patients with a painful tumor reported a significant benefit in less than 3 hours. After 30 days there is a long-lasting plateau of NRS value, likely the clinical response.
Patients were always discharged with an analgesic drug, if necessary. Drug was paracetamol if NRS at discharge was lower than 2; if NRS was higher than 2, patient was discharged with a combination of paracetamol and codeine. At the control visit after one week, 28 of 35 patients reported that they did not take any medication for pain. Further, most of patients, when they were questioned, said they would repeat the treatment if necessary.
Discussing the correlation between tumor characteristics and clinical response, principal independent factors are tumor histotype, size (evaluated as maximum diameter), and setting of tumor. Regarding setting tumor, we define it nodular when tumor elevates from skin or it growths in the subcuticular layer without ulceration of skin; we define flat the tumor that is like a "macula". Ulceration is defined as the complete loss of epidermis above the tumor, with or without any secretion. Deep tumor is used when neoplasia is located under muscle fascia. As reported in table 1, there is no substantial differences in term of clinical response between NMSK, melanoma and breast. The fourth category, listed as "other", includes 3 kind of tumor, with a great difference in term of size and deepness; for this reason, the analysis is not valuable. Nodular and flat tumor are the main responders, while ulcerated and deep tumors register a lower regression. Size is also a great predictive indicator of clinical response. As previously seen in literature, tumors sizing less than 2.0 cm have a high rate of objective response. On the contrary, while tumor size increases, objective response rate dramatically decreases. Lection learnt is double. Treatment should be administered when lesions are smaller, eventually numerous. Secondly, ECT could be used for great tumors as a pure palliative treatment (e.g. bloody mass), or as a neoadjuvant treatment, to reduce the neoplasia and to make it resectable.
Finally, ECT is an unconventional surgical treatment. The first key adjective is "translational". General and plastic surgeons, dermatologists, medical oncologists, and other medical professional figures could have this kind of weapon in their own portfolio. Melanoma and NMSC are the best studied pathologies treated with ECT, but in the future clinical application should be extended to other tumors. The rational of the electroporation can be translate to non-cutaneous solid tumor, inside clinical trials. This is a mirror of modern medicine, in which patient's health is evaluated in a multidisciplinary way, and a promising medical treatment (e.g. antiPD1 drugs) could be applied successfully to a spectrum of malignancies. The second key adjective linked to ECT is "simplicity". Skills required are simple and, after few treatment, the methodology is often acquired. The only concept not to be forgotten is that every clinical case should discussed with all the specialists involved in the treatment, to verify if ECT is really the best treatment, for that patient and in that moment. According to this sentence, ECT should be performed in centers with a proven experience in oncological treatment.

## CONCLUSION

On the basis of this study, ECT is a safe and feasible treatment. Learning curve is fast and clinical results are encouraging. Tumor histotype is not related to response; on the contrary, tumors measuring less than 2 cm have a better outcome; on the contrary size tumor bigger than 3

cm is a negative indicator for clinical response. Preliminary multidisciplinary discussion is mandatory to have a significant good outcome. On the basis of the experience with cutaneous treatment, other trial about the use of ECT for other kind of solid tumors should start.

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**APPENDIX A**
Correlation between demographic and pathological data and clinical response according to RECIST

| Demographic and pathological data | | 30 days clinical response | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | N | CR | % | PR | % | OR (%) | SD | % | PD | % |
| **Sex** | | | | | | | | | | |
| Male | 13 | 4 | 31 | 8 | 61 | 92 | 1 | 8 | 0 | 0 |
| Female | 22 | 11 | 50 | 8 | 36 | 86 | 1 | 5 | 2 | 9 |
| **Age (years)** | | | | | | | | | | |
| < 40 | 1 | 1 | 100 | 0 | 0 | 100 | 0 | 0 | 0 | 0 |
| 40 - 59 | 4 | 2 | 50 | 1 | 25 | 75 | 1 | 25 | 0 | 0 |
| 60 - 79 | 17 | 7 | 41 | 9 | 53 | 94 | 1 | 6 | 0 | 0 |
| ≥ 80 | 13 | 5 | 39 | 6 | 46 | 85 | 0 | 0 | 2 | 15 |
| **ASA score** | | | | | | | | | | |
| 1 - 2 | 16 | 9 | 57 | 5 | 31 | 88 | 1 | 6 | 1 | 6 |
| 3 - 4 | 19 | 6 | 32 | 11 | 58 | 90 | 1 | 5 | 1 | 5 |
| **Histotype** | | | | | | | | | | |
| Melanoma | 18 | 7 | 39 | 10 | 56 | 95 | 0 | 0 | 1 | 5 |
| NMSK | 6 | 3 | 50 | 2 | 34 | 84 | 1 | 16 | 0 | 0 |
| Breast | 7 | 4 | 57 | 3 | 43 | 100 | 0 | 0 | 0 | 0 |
| Other | 4 | 1 | 25 | 1 | 25 | 50 | 1 | 25 | 1 | 25 |
| **Setting of tumor** | | | | | | | | | | |
| Nodular | 19 | 6 | 32 | 12 | 63 | 95 | 0 | 0 | 1 | 5 |
| Flat | 10 | 7 | 70 | 3 | 30 | 100 | 0 | 0 | 0 | 0 |
| Ulcerated | 4 | 1 | 25 | 1 | 25 | 50 | 1 | 25 | 1 | 25 |
| Deep | 2 | 1 | 50 | 0 | 0 | 50 | 1 | 50 | 0 | 0 |
| **Max diam of tumor** | | | | | | | | | | |
| 0 - 1.0 cm | 6 | 6 | 100 | 0 | 0 | 100 | 0 | 0 | 0 | 0 |
| 1.1 - 2.0 cm | 6 | 4 | 67 | 2 | 33 | 100 | 0 | 0 | 0 | 0 |
| 2.1 - 3.0 cm | 10 | 3 | 30 | 6 | 60 | 90 | 0 | 0 | 1 | 10 |
| > 3.0 cm | 13 | 2 | 15 | 8 | 62 | 77 | 2 | 15 | 1 | 8 |
| Mean rate of response (%) | | | 48 | | 37 | 85 | | 9 | | 6 |

NMSC: Non-Melanoma Skin Cancer
CR: Complete Response
PR: Partial Response
OR: Objective Response
SD: Stable Disease
PD: Progression Disease