O MUNDO DA SAÚDE

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Electrochemotherapy, a new therapy for patients with skin cancer in Latin America: literature review

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Abstract

Electrochemotherapy is an innovative technology used to treat skin and mucosal cancers. It consists of intravenous administration of bleomycin followed by the application of electroporation pulses to the tumor at its margins. These pulses induce the formation of pores in the cell membrane, increasing the cytotoxic efficacy of bleomycin by more than 1,000-fold. As electroporation is a physical phenomenon, different types of tumors can be treated regardless of their histology. Generally, only one treatment session is needed to obtain a satisfactory response. Electrochemotherapy is a good option for recurrent tumors in which other therapies do not provide a response. Additionally, tumors can be shrunk with therapy, allowing for less aggressive surgeries and improving outcomes. Many treatment guidelines have begun to include the use of this non-ablative technique as a new treatment option when other therapies have failed or been rejected by the patient. Treatment is carried out on an outpatient basis with high response rates and few side effects.

Keywords: Cancer. Dermatology. Electroporation. Surgery. Palliative.

INTRODUCTION

Cancer is one of the main causes of death worldwide, and its incidence has increased in recent years. In particular, skin cancer is the most frequent type of cancer, which has a high rate of morbidiy and mortality. When detected early, there are several treatment modalities that are very effective and well tolerated by patients. However, in advanced stages, cure rates are reduced, and limited treatment options often come with many side effects[1]. For this reason, new approaches are needed for patients with relapsed disease or in advanced stages of it. In this context, electrochemotherapy (ECT) emerges, a new local treatment modality that combines the administration of bleomycin or cisplatin with specific electrical pulses to induce cell membrane permeabilization[2]. Indications for this therapy were established after the publication of the In particular, skin cancer is the most frequent type of cancer, which has a high rate of morbidiy and mortality (ESOPE) study in 2006[3] and were updated in 2018[3,4]. Its use in Latin America began in 2020, following the recommenda-

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tions of the previously mentioned guidelines. Therefore, the objective of this study was to carry out a review on electrochemotherapy, present the fundamentals of the technology, the latest results of its use and future perspectives, focusing on Latin America.

Brief History of Electrochemotherapy

The term ECT was first introduced by Mir *et al*. in 1991, describing this new technology and demonstrating the increased efficacy of bleomycin through its combination with electrical pulses to treat tumors in mice[5]. In the same year, the first clinical trial was carried out. The authors treated permeation nodules of squamous cell carcinoma located in the head and neck region, obtaining very good results and few side effects[6]. After this publication, more than 1,000 articles were published about this new technology, using different parameters of pulses, electrodes, medications and doses, correlating the different efficacies and side effects. However, its use was limited to clinical trials, as no electroporation device (electroporator) had been approved. In 2006 the *Cliniporator* (Igea, Carpi, Italy) was approved for clinical use, marking the beginning of a new era in electrochemotherapy as a standard of care[3]. Standard operating procedures published in 2006 established consensus on the ideal electrical pulses for this therapy and the medications to be used, *i.e.*, bleomycin (intratumoral or intravenous) or cisplatin (intratumoral only). In 2008, the International Network for Sharing Practices on Electrochemotherapy (InspECT) database was created to collect information on treatment outcomes across different centers in Europe[7]. In Latin America, its use began in veterinary medicine, mainly in the context of scientific research, principally with two groups, one in Brazil and the other in Argentina. Recently, a new electroporator was approved for clinical use in Argentina, the *OncoPore* (*BIOTEX SRL*, Buenos Aires, Argentina), allowing the use of ECT in the clinical setting for the first time in the region[8].

MATERIALS AND METHODS

To carry out this bibliographic review, the search engines PubMed and Google Scholar were used, during the months of August and September 2023. The keywords electroporation and electrochemotherapy were used, and the most relevant articles were selected, that is, those that were most cited, as well as those published in the last 10 years. Only articles in English, published in international refereed journals, that met the recommendations of the ESOPE were included.

Technology Description

Reversible electroporation

ECT is based on the phenomenon of reversible electroporation. Electrical pulses delivered to tissues induce the formation of an electrical field that produces transient pores that do not affect cell viability. For this reason, the elimination of cancer cells depends on the medication used. This tissue permeabilization allows the cytotoxicity of bleomycin to increase more than a thousand-fold[9].

Saving normal tissues is one of the main advantages of ECT, as large margins, needed in surgical resections, can be treated without compromising organ function and providing excellent cosmetic results without compromising the effectiveness of the treatment.

Electroporation pulses are generated by an electroporator and delivered via an electrode. To be effective, electrical pulses must be applied meticulously throughout the tumor volume, including safety margins. This occurs because the electric field generated by the electroporator is only effective in the area between the needles or plates. The electric field forms the pores and thus facilitates the entry of bleomycin. This field decays quickly outside the electrode and, for this reason, leaving areas untreated can lead to recurrence. Common electrodes include plates and needles. Plates are best suited for extensive, very su-

perficial lesions, while needles are preferred for all other cases. Electrodes are generally chosen according to the location and size of the tumor[9,10] (see Figure 1).

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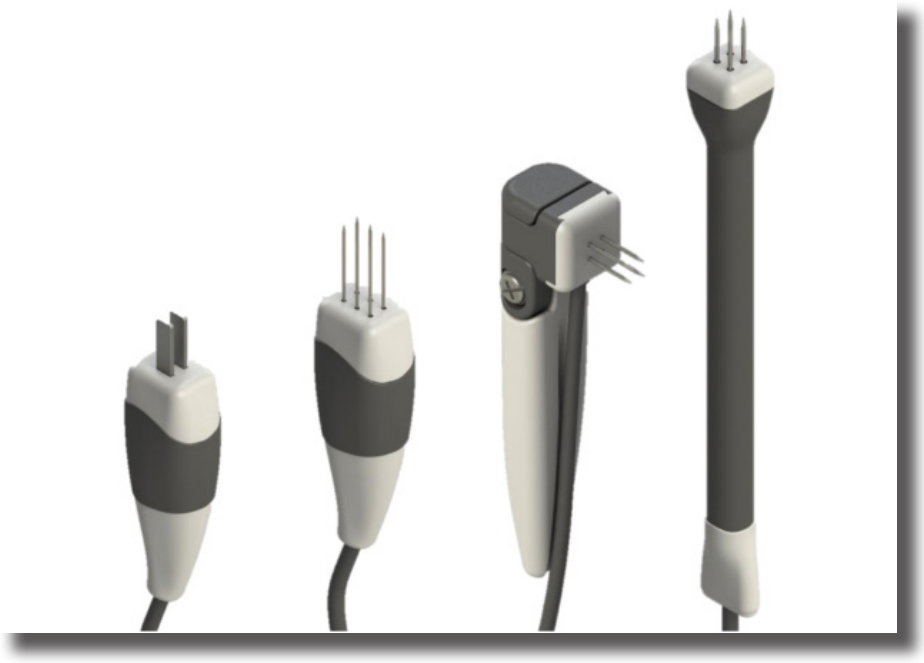

Figure 1 - Different electrodes used for treatment.

Medication used

Bleomycin and cisplatin are the only well-established medications for ECT. Bleomycin is the most commonly used drug, generally applied intravenously, but can also be applied intratumorally, while cisplatin is only used intratumorally. The main reason to prefer intravenous bleomycin is that extensive lesions can be treated, including safety margins, and at the dose used (15,000 IU/m^2 of body surface area), side effects are negligible. However, a maximum cumulative dose of 400,000 IU/m^2 may impede treatment, as the risk of pulmonary fibrosis begins to increase[11]. Cisplatin is reserved for small tumors and cases in which bleomycin cannot be used[12]. A new treatment modality called calcium electroporation uses calcium instead of the aforementioned medications, showing promising results for selected cases[13].

Vascular-lock

It is a physiological phenomenon characterized by the local constriction of vessels in the treated area, secondary to the delivery of electrical pulses, providing the following benefits to the treatment. On the one hand, it reduces blood flow to the treated area, causing tumor starvation. On the other hand, the medicine used is retained in the tumor, increasing its effectiveness. And finally, it allows the treatment of hemorrhagic tumors or highly vascularized regions of the body without bleeding complications[14].

ECT-induced response

In the studies evaluated, the response criteria used are the RECIST criteria, applied

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only to local response[15]. The size of the lesion is assessed by the sum of its largest diameters.

The response criteria are defined as:

Complete Response: Complete remission of the disease locally.

Partial Response: Reduction of more than 30% of the initial size.

Stable Disease: Reduction of less than 30% or growth of less than 20% of the initial lesion.

Progressive Disease: Growth greater than 20% or appearance of new lesions in the treated area.

Objective Response: Sum of partial and complete responses.

RESULTS

The review made it possible to select 28 articles that are presented below.

In ECT, the immune system plays a fundamental role in the final response to the treatment. This response is induced by the phenomenon of electroporation and by the use of bleomycin. This constitutes a solid justification for choosing the use of bleomycin over cisplatin in the treatment. After ECT, the tumor is infiltrated by immune system cells, which subsequently migrate to the lymph node, causing the activation of monocytes and T lymphocytes, resulting in the immunogenic death of the tumor. However, this activation is not intense enough to induce a systemic response in untreated lesions[8].

The improvement of the immunological response triggered by ECT has aroused great interest in the scientific community in recent years[16]. Combining ECT with gene electrotransfer, another electroporation-based treatment, has demonstrated promising results in improving response to ECT and extending progression-free survival in canine models[17].

The studies conducted by Milicevic *et al.*[18] on the use of ECT in patients with immunodeficiency, especially in transplant patients, showed that not only was the treatment safe, but also effective in this type of patients. The authors describe that the innate immune response was trained through successive ECT treatment sessions, demonstrating that this type of response can be adapted to attack cancer cells.

Another promising treatment combination is ECT associated with immunotherapy, in particular with pembrolizumab, in the treatment of patients with advanced-stage melanoma[19], as will be described later.

Current Uses

Currently, ECT is a therapy of great value for dermatologists, plastic surgeons, oncologists, head and neck surgeons, among other medical professionals. It is important to highlight that ECT can be used alone, as a single treatment, or in combination with other therapies. That is, to reduce the size of the tumor before surgery (neoadjuvant), after surgery to eliminate a possible recurrence (adjuvant), or even to treat a recurrence (salvage therapy). It is also possible to treat radioresistant recurrences with good results. As will be presented later, it can be combined with chemotherapy and immunotherapy, improving the results of these therapies[13].

According to the updated standard operating procedures for electrochemotherapy published by Gehl *et al.*, indications for treatment include:

1. Skin metastases of any histology that are symptomatic due to bleeding, ulceration, exudation, odor, or pain.
2. Progression of skin metastases, when symptoms as listed above are expected to develop.

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3. Primary skin cancers, including recurrent tumors, in which other treatment modalities (surgery, radiotherapy, and systemic therapies) have failed or are not feasible.

4. Patients who are receiving systemic therapy but in whom cutaneous metastases are progressing or unresponsive despite a satisfactory response to systemic therapy in internal organs.

5. Patient preference for ECT, after all other treatment possibilities have been fully explained to the patient.

These indications were formulated based on scientific evidence and the clinical experience of experts in the field[4].

Results in Different Histologies

Basal cell carcinoma

It is the most common type of skin cancer, and its incidence continues to increase. The prevalence among the elderly is higher than in the rest of the population, increasing the need for new treatment options for patients who are unsuitable or unwilling to undergo current therapies. In a prospective randomized clinical trial comparing ECT versus surgery, and follow-up for five years, the authors reported a recurrence rate of 2.5% for surgery and 12.5% for ECT. However, this difference was not statistically significant[20]. These results were confirmed in a systematic review, reporting a complete response rate of 92% across 65 studies, with a low risk of recurrence[21]. Another study by Campana *et al.* retrospectively collected ten years' experience, reporting a complete response rate of 72.5% after one session of ECT and 85% after the second session. The five-year recurrence rate in this case was 20% for local disease and 38% for locally advanced disease[22]. The use of ECT for the treatment of this type of cancer has been included in the National Institute for Clinical Excellence (NICE) guidelines in England[23].

Squamous Cell Carcinoma

It is the second most common skin cancer, presenting a high risk of recurrence, generally associated with a poor prognosis. ECT is a good treatment option for cases where surgery and radiotherapy are not viable. In a study by Bertino *et al.*[24], who carried out an analysis in 18 European centers from 2008 to 2020, and the results showed a complete response rate of 62% and a partial response rate of 21%. The authors also report a better response rate in small tumors (<3 cm) and with the use of intravenous bleomycin.

In patients with advanced-stage disease, ECT may be more effective than other treatment options. In a retrospective study carried out by Di Monta *et al.*[25], the authors reported an objective response rate of 81% in patients with stage III disease. They found that ECT can be repeated without affecting patients' quality of life. Furthermore, even when a partial response was obtained, pain and bleeding were reduced, improving the quality of life of these patients. Treatment of primary squamous cell carcinoma has been included in the NICE guidelines[26].

In a study carried out by Jamsek *et al.*[27], it has been reported that using a lower bleomycin dose of 10,000 IU/m^2 compared to the usual dose of 15,000 IU/m^2 can provide similar response rates. However, it is important to note that the recurrence rate was higher in the reduced dose bleomycin group.

In Figure 2, a patient with squamous cell carcinoma was treated, obtaining a complete response.

Melanoma

The incidence of melanoma has increased and its prognosis depends on early detection and immediate treatment, which is still challenging for oncologists and distressing for patients. In this context, ECT is a valuable treatment option for patients with metastatic melanoma who are refractory or ineligible for systemic therapy, or who require rapid palliation of the disease[28]. In a prospective cohort study of 151 patients with metastatic melanoma, a complete response rate of 58% was reported. It was discovered that tumors less than 3cm, adequate coverage of deep

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margins and previous irradiation were associated with better treatment results[29]. ECT is often used as a palliative treatment approach to reduce symptoms and improve quality of life. In a meta-analysis carried out by Petrelli *et al.*[30], a combined objective response rate of 77.6% was reported. ECT is now implemented in the NICE guidelines[31] and in the European Society of Medical Oncology (ESMO) melanoma guidelines[32].

In the specific case of melanoma, the combination of ECT with immunotherapy has shown very encouraging results. Very promising results were presented in the work of Campana *et al.* for the combination of Pembrolizumab with ECT in patients with stage IIIC-IV Melanoma. In this retrospective comparative study, the authors report an increase of: 39% in local response rate, 35% in local progression-free survival at one year, 25% in progression-free survival at one year, and 24% in overall survival at one year, when comparing ECT+pembrolizumab versus pembrolizumab alone (Figure 3)[19].

Figure 2 - Patient with squamous cell carcinoma in the frontal region treated with ECT. Before ECT (left) and 46 days after a single ECT session (right). A complete response was obtained.

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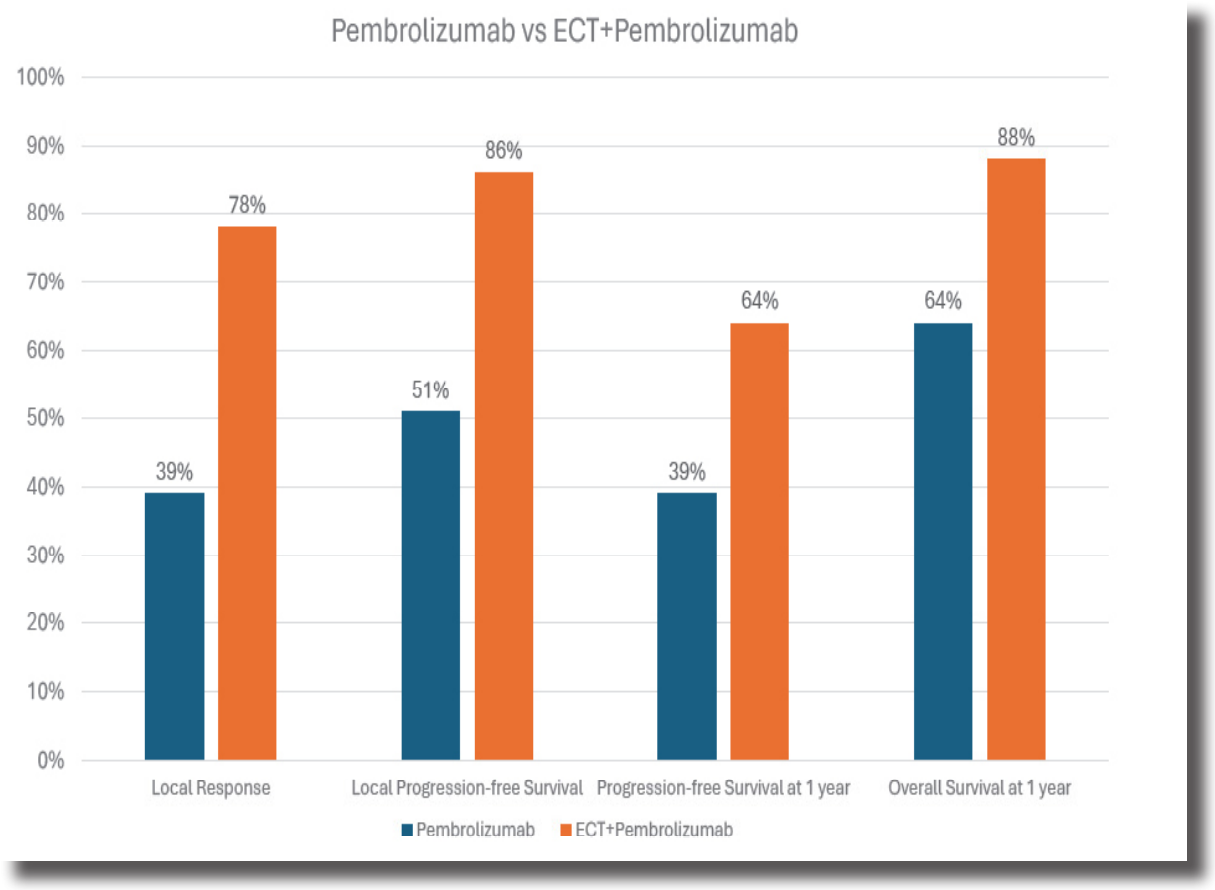

Figure 3 - Results of the combination of ECT with pembrolizumab when compared with pembrolizumab alone. Figure made with data from the work of Campana *et al.*[19].

Other histologies

Because ECT can be used regardless of tumor histology, other less common tumor types can also be treated. It is a treatment option for Kaposi's Sarcoma; in a recent review, patients had a complete response rate of 65-100%, and the treatment was well tolerated[33]. Furthermore, benign lesions such as keloids and hypertrophic scars can be treated with ECT with very good results[34].

Future Uses

ECT is primarily used to treat skin and mucosal cancers, however, this technique is not limited to these areas. In recent years, ECT has proven useful in other regions, such as in the treatment of solid organs, bones, brain, among others. It can even be used during surgery or percutaneously for minimally invasive treatment of deep-seated tumors. For this reason, it is expected that there will be guidelines for the treatment of internal organs in the near future. Among the most promising applications there are the following:

Liver tumors

It has been evaluated in phase I and II clinical trials in humans. It is useful for cases where surgery is not possible. It was used not only for primary tumors but also for liver metastases. The results were very promising, with a very favorable safety profile, mainly because it does not damage blood vessels or liver ducts, unlike thermal ablation therapies. The most interesting aspect is that ECT was suitable for lesions measuring more than six centimeters and close to vital structures, which are very difficult to treat with other therapies[35].

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Pancreatic tumors

Pancreatic adenocarcinoma is a very aggressive tumor, with a very poor prognosis and limited treatment options. A study by Izzo *et al.* demonstrated good performance of ECT in patients, controlling local disease and symptoms in locally advanced pancreatic cancer. Patients treated with variable geometry electrodes had a mean overall survival of 12 months[36].

Bone metastases

Bone involvement significantly affects the quality of life and prognosis of cancer patients. A recent article reported the treatment of 250 bone lesions using ECT, involving 246 patients. Notably, pain assessed by Visual Analogue Scale before ECT was 6.9, which drastically reduced to 2.7 after treatment. Furthermore, adverse events were observed in 3.4% of patients. These findings strongly suggest that ECT may represent an effective therapeutic option for controlling pain from bone metastases.

Spinal cord compressions

A very promising new application of ECT is the treatment of spinal cord compressions secondary to metastatic disease. In recent work by Deschamps *et al.*, they showed relief of neurological symptoms and pain, with an objective response rate of 77% in the first month. The reported side effects were acute radicular pain in 25%, prolonged radicular hypoesthesia in 10%, and paraplegia in 7.5% of cases[37].

Vulvar carcinoma

In a study by Perrone *et al.*, they treated 51 patients with heavily treated vulvar squamous cell carcinoma (surgery, chemotherapy, and radiotherapy), obtaining 65% objective responses. They reported a median progression-free survival of more than 15 months[38].

The Situation in Latin America

Latin America has been very active in the area of ECT research, both in the basic and applied fields. Translational medicine has been the basis for the development of ECT applications in human medicine in Latin America, as veterinary medicine is far ahead in terms of availability. ECT in veterinary medicine is available in most Latin American countries, while ECT for human patients is only available as a standard of care in Argentina. The beginning of ECT in Latin America can be attributed to research carried out in Argentina and Brazil, with many scientific publications and great contributions to knowledge in the field. ECT in veterinary medicine has spread rapidly in the region mainly for two reasons. One of them is the availability of electroporators and electrodes suitable for veterinary patients, available throughout Latin America. The other is the availability of training courses in Spanish and Portuguese. These courses were supported by the International Society for Electroporation-Based Technologies and Treatments (ISEBTT), making them internationally valid. Furthermore, the translation into Spanish and Portuguese of one of the fundamental books on electroporation-based treatments allowed healthcare professionals to access solid information in their native language for free[1].

Replicating the success in veterinary medicine, human medicine is following the same footsteps. The first is the availability of a medical grade electroporator (*OncoPore*, *BIOTEX SRL*, Argentina, approved by the Argentine regulatory agency: ANMAT), which allows treatment upon medical indication, without the need for a clinical trial. The second step is the availability of a training course in Spanish for doctors[2], which aims to provide information on the fundamental aspects and recommendations for its successful application. This course is also supported by ISEBTT. Additionally, medical students receive instruction in ECT during their training at the *Instituto Universitario de Ciencias de la Salud*, *Fundación H.A. Barceló*, ensuring that future doctors are aware of the technology and understand its indications. The availability of treatment in Argentina is expanding rapidly; at the time of writing, three public hospitals (the *Hospital de Agudos JM Ramos Mejia*, Buenos Aires, the *Instituto de Oncologia Angel H Roffo*, Buenos Aires, and the *Hospital de Agudos Petrona V de Cordero*, San Fernando) and two private institutions (the *Clínica Adventista de Belgrano*, Buenos Aires, and the

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Sanatorio Otamendi, Buenos Aires) are already treating their patients with ECT

(footnote
1- http://book.ebtt.org/.
2- http://curso.electroquimioterapia.com.ar/)

ECT is mainly used in Argentina by dermatologists and plastic surgeons, as skin cancer is the most common type of cancer. Skin cancer has been established as a crucial part of the development of ECT due to the accessibility of tumors and the need for new therapies for selected patients who are not candidates for first-line therapies. It should be noted that ECT does not compete with other therapies, as first-line therapy should be performed whenever possible. The high response rates of ECT combined with the excellent aesthetic results obtained so far have been very helpful in building confidence in the technique. Another important aspect of ECT is that only one treatment session is usually performed, sparing patients with limited life expectancy from lengthy treatments that would confine them to the hospital. This reduces costs for the institution and allows the treatment of more patients with the same resources, a very important aspect for already overburdened healthcare systems in Latin America.

In addition to the standard therapy applied, clinical trials are being designed to translate the results obtained in the laboratory by developing new electrodes that will allow the treatment of different areas of the body that are not accessible to conventional electrodes.

Considering other electroporation-based therapies, the use of gene electrotransfer is being studied to complement the immune response generated by ECT to induce a systemic response to metastatic lesions.

CONCLUSION

ECT for skin cancer presents favorable results in terms of remission for tumors, whether primary or metastatic from other organs, of different histologies that cannot be treated with first-line therapies or have been ineffective. Currently, it is indicated when first-line therapies are not applicable, have failed or are rejected by the patient. As a new technology, it is essential to disseminate information about ECT and its results in courses, congresses and scientific meetings to extend its use throughout Latin America. This new therapy can benefit patients at an advanced stage of disease or patients with high morbidity rates that preclude conventional treatment, achieving complete remission or relief of the main symptoms when conventional therapies no longer work.

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