Electrochemotherapy of Head and Neck Cancer

Marco Benazzo, Giulia Bertino, and Ales Groselj

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Abstract

In the head and neck area, electrochemotherapy (ECT) is currently implemented for the treatment of recurrent and/or metastatic cutaneous, subcutaneous, mucosal, or deep-seated tumors of any kind of histology. However, its particular efficiency in the treatment of small, primary, and treatment-naïve tumors has already been demonstrated. Nevertheless, ECT has different effectiveness in tumors of various histotypes. Basal cell carcinomas proved to be a most responsive tumor with almost 100 % objective response rate and excellent cosmetic results without any functional impairment of treated sites. For the treatment of deep-seated tumors in the head and neck region, long single needle electrodes are used. These electrodes can be placed in various patterns with the aim to cover large and irregular-shaped tumors, hidden under the visible surface. Moreover,

M. Benazzo • G. Bertino (✉)
Department of Otolaryngology Head & Neck Surgery, University of Pavia, IRCCS Policlinico San Matteo Foundation, Pavia, Italy
e-mail: m.benazzo@smatteo.pv.it; giulia.bertino@tin.it

A. Groselj
Department of Otorhinolaryngology and Cervicofacial Surgery, University Medical Centre Ljubljana, Ljubljana, Slovenia
e-mail: ales.groselj@kclj.si

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coupling treatment planning and navigation system enables precise insertion of long, single needle electrodes into deep-seated tumors of the head and neck region. Further developments in the application of ECT in the head and neck cancers are orientated to reduced dose of bleomycin in elderly patients and combining ECT with immunotherapy and/or immunogene electrotransfer.

Keywords
Electrochemotherapy • Head and neck cancer • Palliative treatment • Basal cell carcinoma • Squamous cell carcinoma • Malignant melanoma • Variable geometry electrodes • Navigation system • Immunogene electrotransfer

Introduction

The first clinical evaluation of electrochemotherapy (ECT) with bleomycin in patients affected by head and neck cancers was performed in 1991 at Institut Gustave-Roussy (Villejuif, France) (Mir et al. 1991a).

The results of this study confirmed the safety and the feasibility of ECT in humans. Other authors have since then confirmed the efficacy of ECT in the head and neck region, but their results were not completely comparable because of the use of various not standardized treatment protocols (Reinhold 2011). The widespread popularity of ECT had been obtained after the multicentric European Standard Operating Procedures of ECT (ESOPE) study in 2006, which established the standard operating procedures of ECT for clinical use (Marty et al. 2006).

In two different case series of nonmelanoma skin cancer in head and neck region, Gargiulo et al. (2010, 2012) reported rates of objective response (OR) and complete response (CR) were 100 % and 72–80 %, respectively. Given their results, the authors suggested a possible neoadjuvant role for those cases in which standard treatments would be too demanding for the patient.

Mevio et al. (2012) acquired similar results (94 % OR and 62 % CR) in a clinical study involving a total of 31 nodules in 15 patients affected by primary/recurrent nonmelanoma skin and mucosal head and neck cancer. Moreover, they found that small nodules (<3 cm) were responding better to treatment with ECT. Consequently, they suggested a possible future role of ECT as primary treatment of small head and neck cancers. These results and conclusions were similar to those previously published by Landström et al. (2010), who reported 66 % of CR and proposed the application of ECT as a treatment option for basal cell carcinoma. In their latter study, the same authors (Landström et al. 2015) also compared the efficacy of ECT alone and ECT followed by radiotherapy for the treatment of squamous cell carcinoma of the oral cavity and oropharynx. According to their report, all six patients submitted only to ECT were alive and free of disease after a 5-year follow-up period. The 5-year disease-specific survival of all 19 patients, treated with ECT only or in combination with radiotherapy, was 75 %. The bias of this study is due to the potential interference of two associated treatments. It is thus impossible to conclude whether the tumor response was mainly due to ECT alone.

Campana et al. (2014) provided further experience with the use of ECT for the treatment of skin and mucosal nonmelanoma head and neck cancer. They reported an OR and a CR of 59 % and 38 %, respectively. Moreover, they demonstrated that tumor response was significantly better in small, primary, and chemo-naïve patients.

The last most comprehensive paper up to date, which analyzed the efficacy of ECT in head and neck area, was recently published by Bertino et al. (2016). This multicentric prospective nonrandomized clinical study evaluated the efficacy, pain control, quality of life, and short-term survival in a group of 99 patients submitted to ECT for melanoma and nonmelanoma skin cancer of the head and neck. The most responsive tumor was basal cell carcinoma (OR 97 %; CR 91 %), followed by squamous cell carcinoma (OR 79 %; CR 55 %) and malignant melanoma (OR 77 %; CR 55 %). Tumor response was significantly dependent on the size of the nodules, whether it was a primary or recurrent tumor and whether it was previously treated. In particular, small (<3 cm), primary, and treatment-naïve tumor nodules showed significantly higher percentages of objective response respect of large (>3 cm), recurrent, or previously treated nodules. Moreover, for recurrent or metastatic nodules, tumor response was correlated to the number of previous treatments (better after surgery only, instead of multiple treatments). ECT significantly relieved pain during follow-up and, thus, improved the quality of life, as demonstrated by the significant reduction of the percentage of patients taking pain medications and improvement of the scores of the three quality of life questionnaires (EQ-5D, QLQ-C30, and QLQ H&N35) employed. The 1-year overall and T-specific survivals were 76 % and 89 %, respectively. According to these results, the authors proposed conducting clinical trials to consider ECT as a first-line treatment for small, primary skin cancer, with special focus on basal cell carcinoma (Figs. 1, 2, 3, and 4).

Current Role of Electrochemotherapy in Head and Neck

ECT is currently used as palliative local treatment of recurrent/metastatic tumor nodules of any histology in patients not suitable for standard treatments, to control the bleeding lesions and relief of pain due to the tumor mass. These pathological conditions can be particularly severe and devastating in patients with head and neck cancer. The standard treatments usually employed can add to additional disability, thus worsening the remaining quality of life in these patients. Conversely, ECT in head and neck cancer patients results in a minimal or nil function impact and leads to healing of treated tumor lesions without damage to the surrounding healthy tissues (Cadossi et al. 2014; Salwa et al. 2014).

ECT has been provable effective in small nonmelanoma skin cancers, with percentages verging on 100 % for basal cell carcinoma (Gargiulo et al. 2010, 2012; Landström et al. 2010; Bertino et al. 2016) after a single treatment session. The treatment of oral and oropharyngeal lesions is more complex than ECT of

Fig. 1 An 88-year-old woman with two BCC lesions (recurrent on the forehead and primary on the neck); multiple comorbidities and Alzheimer disease. Treatment: two ECT sessions with i.v. bleomycin and hexagonal electrode under general anesthesia. *Top*: preoperative; *bottom*: 1-year F-U (small residual disease on both lesions)

Fig. 2 A 93-year-old woman with primary SCC; multiple comorbidities and Alzheimer disease. Treatment: one ECT session with i.v. bleomycin and finger electrode under local anesthesia and sedation. *Left*: preoperative; *right*: 1 year F-U (complete response with minimal loss of tissue)

Fig. 3 A 63-year-old man with primary SCC of the nose; previously submitted to total laryngectomy for SCC. Treatment: two ECT sessions with i.v. bleomycin and row-needle electrode under local anesthesia + sedation. *Left*: preoperative; *right*: 8 months F-U (complete response)

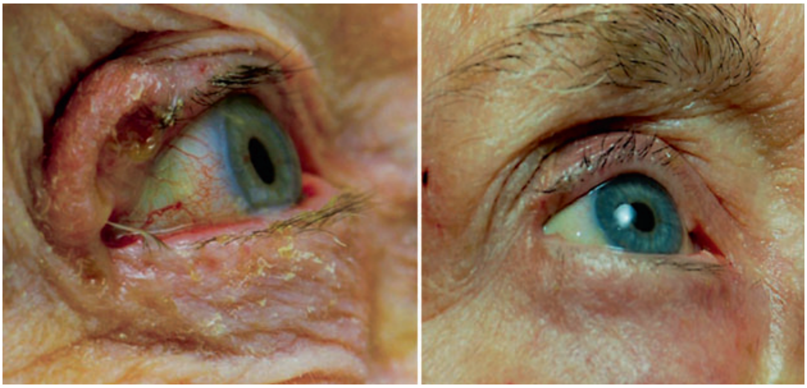

Fig. 4 A 90-year-old with basal cell carcinoma on the lateral side of right upper eyelid; multiple comorbidities. Treatment: one ECT session with intratumoral bleomycin and row-needle electrode under local anesthesia and sedation. *Left*: preoperative; *right*: 4 months F-U (complete response)

cutaneous and subcutaneous nodules, since for effective antitumor response of ECT two conditions have to be met: sufficient amount of drug molecules present in the tumor and adequate tumor coverage by the electric field. In general, 400 V/cm with 8 × 100 μs pulses are required for the tumors and can be obtained with the use of appropriate electrodes and pulse generator. Thus, complete response of small nodules can be achieved with standard or finger electrodes in easily attainable areas (oral cheek, mobile tongue, the floor of the mouth, internal lip). Larger nodules with peculiar growth pattern or particular location (tongue base, oropharynx) cannot be entirely reached with fixed geometry electrodes and thus covered by sufficient electric field. Consequently, the treatment outcome is compromised (Campana et al. 2014; Landström et al. 2015). New devices are under development to improve the possibility to completely electroporate the nodules located in these particular areas.

All the subcutaneous metastatic neck masses can theoretically be treated with ECT; problems could emerge when they are bulky or near the major vessels. The treatment of bulky lesions may require multiple sessions since the maximal length of the standard electrodes is 3 cm. Multiple treatments can lead to massive necrosis and severe pain after the treatment. Moreover, if the lesion is infiltrating the wall of the major vessels, the necrosis may result in massive and potentially fatal bleeding from vessels' blowout.

With some technological modifications, ECT is also applicable for treatment of deep-seated head and neck tumors, namely, metastases and oropharyngeal tumors in highly selected patients.

The usage of standard electrodes with fixed geometry in ECT of deep-seated tumors in head and neck region has several shortcomings. These tumors are not just hidden under the visible surface, but they are also large with peculiar growth pattern. Complex anatomy in the head and neck region with the proximity of several vital structures (e.g., large blood vessels, cranial nerves), limited space, and bone structures is another possible contributing factor to failure of adequate coverage of the tumor with the sufficient electric field. Consequently, treatment outcome could be jeopardized. In the most cases of deep-seated tumors, fixed geometry electrodes cannot be inserted deep enough to cover the tumor's deep margins. Long single electrodes were developed for ECT of these tumors. These electrodes can be inserted in various patterns deep enough to cover margins of irregularly shaped tumors as well (Groselj et al. 2015).

However, the determination of adequate position for each electrode and sequence of the electric pulses deliverance during the procedure still present a significant challenge. This demerit can be excluded with treatment planning of electrode positioning and electric field simulation before the procedure (Groselj et al. 2015).

The first step of treatment planning is image segmentation of CT and MR images with the aim to differentiate the tumor and surrounding tissue. The segmented CT or MR images are used for creation of a 3D model with electric properties correlating to each tissue in the treatment area.

The next step is defining the position of electrodes and the amplitude between each pair of electrodes, which ensures coverage of the whole tumor (together with safety margins) with the sufficiently high electric field needed for permeabilization of the cell membranes (Pavliha et al. 2012; Marčan et al. 2015).

The hidden visual surface of deep-seated tumors disables orientation in 3D space. Therefore, the percutaneous insertion of single needle electrodes in the operating room can still be imprecise, even after the ideal entry points of each electrode had been calculated. This obstacle can be overcome by coupling treatment plan and navigation system. Navigation system helps the surgeons to locate the tumor during the surgical interventions according to pretreatment CT or MR images and is routinely used during head and neck operations (Groselj et al. 2015).

Before ECT, CT or MR images with marked electrode entry points, previously calculated with treatment planning, are imported into the navigation system. In the next step, entry points for the electrodes on the patient's skin have to be found with the use of navigated pointer consistent with CT or MR images from the navigation

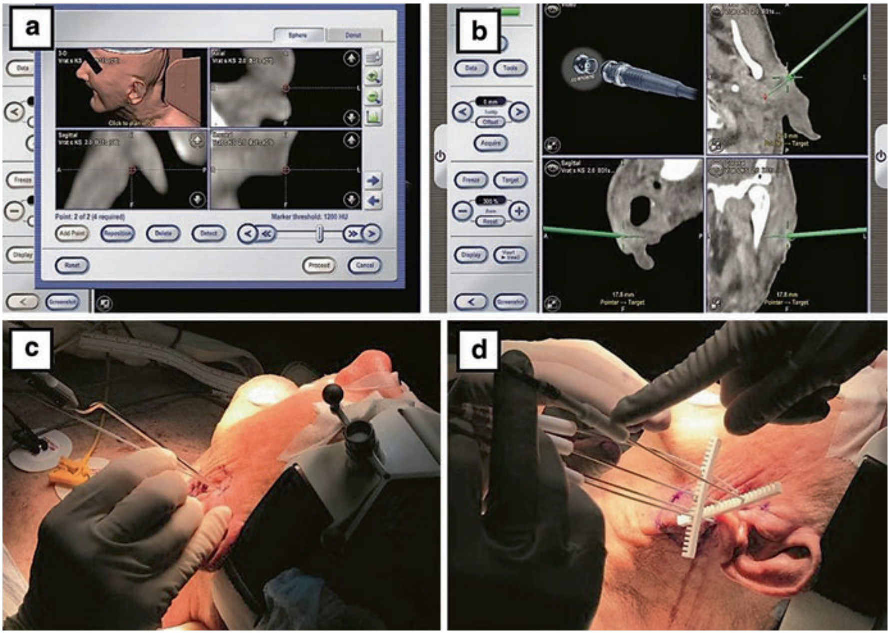

Fig. 5 Treatment 3-D planning and navigation system (**a**). Navigation is used to access the planned skin entry points and direction of electrodes (**b**). Positioning of navigation pointer and first needle electrode (**c**) and the final positioning of all five needle electrodes (**d**)

system. The system itself is also capable of determining the optimal trajectory from electrode's entry point (skin) to target point (tumor). However, the depth of the electrodes cannot be visualized and hence is not well controlled. This obstacle can be bypassed with measuring the length of the electrode penetration from the skin to the tumor (Groselj et al. 2015) or with the use of the electrodes with imprinted ruler.

This technological approach is more time consuming, compared to routine ECT with fixed geometry electrodes, but it is amenable for specific clinical situations with very limited treatment options. Furthermore, with such technological solution and its future improvements, also deep-seated tumors of the head and neck region can be considered as the indication for ECT (Fig. 5).

Indications and Contraindications

In the head and neck area, ECT can be applied to the treatment of cutaneous, subcutaneous, mucosal, or deep-seated tumors of any histology.

The choice of drug delivery (local vs. systemic), the type of anesthesia (local vs. general), and the type of electrodes depend on the number, size, and location of the tumor nodules and the patient's general condition.

Table 1 Treatment modalities for cancers of the head and neck area

Treatment	Site, number, size	Anesthesia	Drug administration	Electrode
Modality A	Head, face	Local ± sedation	Bleomycin i.t/i.v. Cisplatin i.t.	Plate electrode (if superficial) Row-needle, hexagonal, or finger electrodes (if deep)
	<3 nodules			
	<2 cm			
Modality B	Head, face	General	Bleomycin i.v.	Row-needle or hexagonal electrodes
	>3 nodules			
	>2 cm			
Modality C	Cheek, chin, intraoral	General	Bleomycin i.t/i.v. Cisplatin i.t.	Row-needle electrode Hexagonal electrode Finger electrode Variable geometry electrodes
	Any number			
	Any size			

In general, three kinds of treatment modalities can be chosen for head and neck tumors (Table 1).

In case of few (<3) and small (<2 cm) nodules located at the upper part of the face and scalp, the procedure can be conducted under local anesthesia; bleomycin can be delivered either intratumorally or intravenously, cisplatin must be delivered intratumorally only. The choice of the electrode depends on the morphology and depth of the lesion. Performing the procedure under general anesthesia with intravenous route of administration of bleomycin is a preferable option in the cases of a higher number and larger size of the nodules.

When nodules involve the lower face, neck, or oral mucosa, the procedure should always be performed under general anesthesia, due to the possible occurrence of severe pain induced by muscle contraction. In these cases, the route of drug administration will depend on number and volume of the nodules according to SOPs, as well as the choice of electrodes.

Moreover, when the treatment is applied in the oral cavity or oropharynx the possibility of post-operatory swelling of the soft tissues with consequent risk of acute respiratory distress must be taken into consideration; thus, a safety tracheotomy is preferable.

Contraindications to ECT in the head and neck area are listed in Table 2.

Absolute contraindications are tumor invasion of the major neck vessels because of the high risk of carotid or internal jugular vein blowout secondary to tumor necrosis induced by ECT, patient's general conditions impeding general or local anesthesia, allergy to bleomycin/cisplatin, or previous cumulative dose of bleomycin >240,000 IU/m2.

Furthermore, caution must be paid in the treatment of full-thickness lesions of the chin, cheek, or lips because of the high risk of massive necrosis with consequent orocutaneous fistula or labial incompetence.

Table 2 List of exclusion criteria for ECT in the head and neck area

Clinical situation	Absolute contraindication	Relative contraindication
Major vessel tumor infiltration	Macroscopic infiltration of the walls of the internal jugular vein or carotid artery	
Difficulties with local/ general anesthesia	Yes	
Allergy to bleomycin or cisplatin	Yes	
Cumulative dose of bleomycin	$>$240,000 IU/m^2	
Full-thickness lesions of the chin, cheek, or lip		High risk of orocutaneous fistula and/or labial incompetence
Cardiac arrhythmias, pacemaker	Thorax application $<$7 cm	Head neck application ($>$30 cm from heart)
Pulmonary function (Fibrosis)	Bleomycin i.v.	$<$30 % O_2 delivery Bleomycin i.t.
Hematology (PLT $<$70,000/mm^3, INR $>$1,5)		Verify type of electrodes
Renal function (Creatinine $<$150 μmol/l)		Bleomycin i.t. Adequate hydration

The presence of a pacemaker in a head and neck patient is usually just a relative contraindication because the head and neck area is more than 30 cm away from the thorax and thus no effect of the current on the pacemaker is expected. The poor pulmonary function is another relative contraindication that can be overcome by using i.t. bleomycin and by ventilation with a low percentage of oxygen ($<$30 %); the poor renal function can be overcome by using i.t. bleomycin as well or with adequate hydration. Bleeding due to the use of anticoagulants or low platelet count is diminished with the vascular-lock effect of ECT itself and by avoiding multiple sessions. The amount of necrosis progressively increases after each treatment, and the surrounding healthy tissue may not have time for the healing process; as consequences the vessels' disruption and blowout may occur.

Current and Future Perspectives

At present, ECT is considered as local treatment in patients with cutaneous, subcutaneous, mucosal, or deep-seated tumor nodules of any kind of malignant histology and recurrent disease after conventional therapies. It is a feasible treatment option for controlling tumor growth, tumor bleeding, and mass-related symptoms (Gehl and Geertsen 2000; Marty et al. 2006; Matthiessen et al. 2011; Mali et al. 2013; Cadossi et al. 2014).

ECT is particularly useful in head and neck cancer patients because it results in a minimal or null function impact and leads to healing of treated tumor lesions without damage to the healthy tissues. However, much attention must be paid to the intratumoral use of bleomycin in the oral cavity. The toxicity of bleomycin for mucosal tissues is known and can lead to pain and large areas of necrosis when injected locally (Cadossi et al. 2014).

The risk of severe side effects and necrosis can be higher in elderly patients, because of the increased serum levels of bleomycin, induced by the reduction of total body water and a decline in glomerular filtration rate (Groselj et al. 2016). In order to avoid possible complications, Groselj et al. (2016) have proposed a reduced dose of bleomycin (10,000 IU/m2) in elderly patients, instead of the standard dose of 15,000 IU/m2, since the serum clearance curve of bleomycin is slower (less than 500 ml/min) in elderly population.

Several nonrandomized, non-controlled clinical trials have shown ECT to be an efficient and safe treatment also in primary cutaneous or mucosal tumors (Landström et al. 2010, 2015; Gargiulo et al. 2010; 2012; Mevio et al. 2012; Bertino et al. 2016). The reported percentages of objective response are high, ranging from 57 % to 100 %, with the most responsive tumor being basal cell carcinoma (Landström et al. 2010; Bertino et al. 2016). The percentages of short- and long-term disease-specific survival are very promising (89–75 %) (Landström et al. 2015; Bertino et al. 2016). For these reasons, some authors foresee a role for ECT as a first-line treatment of head and neck cancer, particularly in elderly patients, or as neoadjuvant treatment for those cases in which surgical procedures and/or radiotherapy would be too devastating in achieving proper oncological results (Gargiulo et al. 2010, 2012; Landström et al. 2010; Mevio et al. 2012; Bertino et al. 2016).

Nevertheless, despite these results, the future role in the curative treatment of head and neck cancer remains undetermined. In fact, at present, no large randomized clinical trials comparing ECT to the standard treatments of head and neck cancer, namely, surgery and radiotherapy, have been published yet.

Although ECT is highly efficient on treated nodules, it remains a local treatment having no apparent antitumor effects on non-treated distant nodules, even though it has been demonstrated that electroporation induces inflammation of the treated tissue and then activation of the immune system (Calvet and Mir 2016). It has been proposed that ECT might allow tumor antigen shedding, thus attracting immune antigen-presenting cells. This effect was demonstrated in the preclinical study by Mir et al. (1991b) and Sersa et al. (1997), who found that tumor response to ECT was more effective in immunocompetent mice instead of nude mice.

This evidence led to clinical studies in humans; in particular, it has been reported about the treatment of metastatic melanoma nodules with ECT and IL-2 with long-lasting remission of distant metastasis in 20 % of patients (Calvet and Mir 2016).

The combination of ECT and immunotherapy seems to be a future perspective. Such treatment may have a long-term effect on local and systemic cancer eradication. Recently, two studies showed promising results in the treatment with the combination of ipilimumab and ECT (Brizio et al. 2015; Mozzillo et al. 2015). Brizio et al. (2015) have demonstrated that local ECT treatment of cutaneous lesions of melanoma followed by ipilimumab administration resulted in the complete regression of all the cutaneous and visceral metastases over the period of at least 1 year. While Mozzillo et al. (2015) reported about decreased or stable volume of distant non-ECT-treated tumors in 9 patients out of 15, possibly through ipilimumab-induced regulatory T cell depletion.

Similarly, anti-programmed cell death protein 1 (PD1) antibodies are also of great interest as they prevent the inhibitory effect on T cell functions of the interaction between PD1 (on T cells) and PD1 ligand (on tumor cells) (Zitvogel and Kroemer 2012). Hence, a combination of ECT with anti-PD1 antibodies could be an elegant way to destroy the initial nodule while raising efficient antitumor responses to ultimately eliminate remaining and circulating cancer cells (Calvet and Mir 2016).

Alternatively, immune stimulation through electrogenetherapy (EGT) has also raised great hope for the treatment of cancer. In fact, Daud et al. (2008) published the first clinical evaluation of gene electrotransfer of plasmid coding for IL-12 in patients with metastatic melanoma. In this study tumor necrosis and T cell infiltration were observed also in non-electroporated distant lesions with complete regression of all metastases in 10 % of patients, while 42 % displayed a stable disease or partial response.

According to these results, Sersa et al. (2015) recently proposed a model of combination of ECT with peritumoral IL-12 electrotransfer; ECT boosted with immunogene electrotransfer could be considered a sort of in situ vaccination to potentiate not only death of the ECT-treated tumor nodule but also to activate the immune system toward the same tumor cells on distant metastases where it can exert its immunological actions.

Conclusion

ECT is a well-established local treatment providing effective local tumor control and minimal aesthetical or functional impairment. Recent clinical evidence supports ECT use to eradicate smaller lesions, although it has also proven to be effective in palliation of symptomatic lesions and as a neoadjuvant treatment to allow less invasive surgical or radiotherapeutic approaches. The low toxicity and usually minor side effects make it an ideal choice for patients with poor performance status or comorbidities, which may be present especially in elderly people. Moreover, recent clinical evidence supports investigation of ECT application beyond the skin to deep-seated tumors due to the development of the variable geometry electrodes and treatment planning. In the longer term, the combination of ECT with appropriate immunomodulators will enable the translation from a local disease control to a systemic response mediated by the patient's immune system. Furthermore, treatment planning coupled with navigation system for accurate placement of electrodes for execution of treatment plan allows treatment of difficult to reach and deep/protruding tumors in head and neck region.

Cross-References

- ▶ Adjuvant Immunotherapy as a Tool to Boost Effectiveness of Electrochemotherapy
- ▶ Clinical Applications of Gene Therapy: Principles of Gene Electrotransfer
- ▶ Cliniporator: Medical Electroporation of Tumors
- ▶ Combined Treatment of Electrochemotherapy with Immunomodulators
- ▶ Combined Treatment of Electrochemotherapy with Irradiation
- ▶ Electric Field Distribution and Electroporation Threshold
- ▶ Electrochemotherapy and Its Clinical Applications
- ▶ Electrochemotherapy of Basal Cell Carcinoma
- ▶ Electrochemotherapy of Cutaneous Metastases
- ▶ Gene Therapy for Skin Tumors
- ▶ Immune Response After Electroporation and Electrochemotherapy
- ▶ Irreversible Electroporation and Its Clinical Applications
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- ▶ Principles of Electroporation for Gene Therapy
- ▶ Standard Operating Procedures for Electrochemotherapy
- ▶ Tissue Ablation Using Nanoseconds Electric Pulses
- ▶ Treatment Planning for Electrochemotherapy and Irreversible Electroporation of Deep-Seated Tumors
- ▶ Vascular Effects of Electroporation and Electrochemotherapy

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