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HEAD AND NECK

# Electrochemotherapy as palliative care in patients with local or metastatic recurrence of head and neck cancer: review of state of the art

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SUMMARY

Head and neck cancers are mostly represented by squamous cell carcinoma. Despite effective treatment of primary tumours, local recurrences and metastases are frequent, with up to a 60% risk of local and 30% of distant failure. Moreover, second primary tumours sometimes occur in these patients (2-3% per year). Treatment of recurrences, metastases, and second primary tumours can be extremely challenging for Otorhinolaryngologists, especially in patients who have already been treated with radiotherapy, previous surgery, or both. Electrochemotherapy represents an effective and valid option in these cases.

KEY WORDS: electrochemotherapy, metastatic, palliative, head and neck, cancer

## Introduction

Squamous cell carcinoma (SCC) is the most common malignancy Otorhinolaryngologists have to deal with in their daily clinical practice. In metastatic or recurrent SCC, traditional treatments, such as surgery or (chemo)radiotherapy, may be unsatisfactory. As a consequence, treatment of recurrences and second primary cancers remains extremely challenging. Electrochemotherapy (ECT) was first described in the late 1980s and has increasingly gained popularity as a therapeutic tool for head and neck tumours that do not respond to first-line therapeutic approaches. ECT is a local ablative treatment combining the use of systemic or intratumoural drugs (bleomycin, cisplatin) with electroporation (EP), which was developed as an effective, non-invasive, and safe cancer treatment. EP uses a very intensive electric stimulus applied for a short time, causing a localised electric field that enhances the permeability of cell membranes. This stimulates cytoplasmic uptake of hydrophilic antineoplastic agents and increases local cytotoxicity causing apoptosis of cancer cells. Therefore, ECT allows to use a lower dosage of antineoplastic drugs, reducing their potential side effects and resistance. Moreover, ECT mechanisms of action involve immune stimulation and the so-called "vascular lock". Cancer cell lysis during ECT provokes a large recruitment of antigen presenting cells (APCs) from peripheral blood and liberates damage associated molecular patterns (DAMPs) which stimulate an immune reaction. Furthermore, EP and ECT cause vasoconstriction and endothelial cell death in afferent tumour blood vessels, thus reducing its perfusion and decreasing antineoplastic drug washout [1]. Thanks to these features, ECT has been demonstrated to be very useful for treatment of SCC close to vital organs, especially in patients who

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were previously treated with (chemo)radiotherapy or extensive surgery, lowering toxicity and improving both cosmetic results and quality of life.

## Instrumentation

ECT requires a generator of electrical pulse and different types of electrodes. The physical basis of EP is a pulsed electric field obtained through a train of square wave electric pulses of sufficient amplitude. This local electric field is applied to the cancer cells using electrodes. Usually, eight impulses with a duration of 100 μs are delivered at a frequency of 1000-5000 Hz. Voltage is often automatically set by the pulse generator and depends on the number of electrodes, electrode type and geometry [2].

For smaller and superficial lesions, such as skin cancer or metastases, local anaesthesia may be adequate. General anaesthesia, instead, is required for wider tumours and deep seated lesions. However, general anaesthesia is necessary when treating tumours located on the face, scalp, and oropharynx. Because of potential tissue swelling, ECT for oral cavity and oropharyngeal cancers may need elective tracheostomy in order to secure the airways.

*Electrode types*

Different electrode shapes, lengths, and sizes can be used. Choice of the electrode type is based on the site and morphology of the lesion itself: different electrode configurations will be required to cover all its volume with the electric field. Electrode shape can be in the form of plate or needle. Plate electrodes are useful in superficial and skin lesions. They require a higher voltage to allow the electric field to penetrate within deep tissues. Regarding needle electrodes (mostly used for small tumours), they can be positioned in line with a 4-mm distance between them or put with an hexagonal arrangement, which is suggested for lesions larger than 1 cm. Moreover, needle electrodes can be inserted through the underlying soft tissues, with a depth of up to 3 cm. Wearable finger shaped electrodes are also available. Needles on these electrodes can be placed with a longitudinal orientation, protruding from the phalanx (with a needle length of 10-20 mm), or orthogonal orientation below the fingertip (needle length 15 mm). Their aim is to treat small lesions located within anatomical spaces that are difficult to access [3]. The electric field, in fact, is higher in the vicinity of the electrode, while it quickly decreases outside the electrode array. Therefore, it is necessary to move the electrode and place it in different positions in order to adequately treat the entire tumour volume if the lesion is larger than the distance between the electrodes [4].

*Antineoplastic agents*

Hydrophilic and poorly permeant antineoplastic drugs are ideal for ECT. Among all drugs that have been tested to find the best combination with EP, only two have been approved for ECT, namely bleomycin and cisplatin. Cisplatin (2 mg/ml) must be infused intratumourally. Tumours < 0.5 $cm^3$ should be treated with 2 $mg/cm^3$; lesions between 0.5 and 1 cm should be injected with a dose of 1 $mg/cm^3$; a dose of 0.5 $mg/cm^3$ should be used for tumours larger than 1 $cm^3$. Bleomycin can be injected either intravenously or intratumourally. Intravenous bleomycin is injected in a single bolus of 15000 $IU/m^2$ in 30-60 seconds. Intralesional injection should be done in a dose of 1000 $IU/cm^3$ in lesions < 0.5 $cm^3$, 500 $IU/cm^3$ in lesions ≥ 0.5 $cm^3$, and 250 $IU/cm^3$ in tumours ≥ 1 $cm^3$ [5].

For intralesional injections, the application of the electric pulses should be completed in 1-8 minutes after the manoeuver. For intravenous infusion, the electric pulses should be applied to the cancer site during the pharmacokinetic peak, which is known to occur at 8-28 minutes after the injection. ECT application usually results in inflammation, tissue swelling and tumour necrosis. Elective tracheostomy can be therefore required in oropharyngeal and oral cavity ECT due to the associated risk of upper airway obstruction. Follow-up is usually scheduled at 4 weeks after treatment. When needed, a second ECT application can be performed with a 4-week interval from previous treatment with intravenous bleomycin, while it can be repeated whenever necessary for intratumoural injection of cisplatin.

## Indications

Head and neck cancers represent more than 5% of malignancies worldwide, and about 90% of these are SCC. Besides SCC, various other malignancies can occur in head and neck region, such as melanomas, sarcomas, and cutaneous basal cell carcinoma (BCC). These tumours are often diagnosed in an advanced stage and the first-line therapeutic approach is mostly surgery and/or (chemo)radiotherapy. Despite this, loco-regional recurrences and distant metastases are frequent (Fig. 1), with up to 60% risk of local and 30% of distant failure. Moreover, second primary tumours sometimes occur in these patients (with a cumulative incidence of 2-3% per year). Treatment of recurrences, metastases, and second primaries can be extremely challenging for Otorhinolaryngologists, especially in patients who have already been treated with curative intent by other treatment modalities. Only a few cases, in fact, can be treated by re-irradiation, immunotherapy, second-line chemotherapy or salvage surgery, particularly due to the potential loss of function, aesthetic disfigurement, and reduction in quality



**Figure 1.** Right regional and left peristomal recurrences of laryngeal carcinoma after total laryngectomy.

of life typically associated with most, if not all, such rescue therapeutic strategies. This is why there is an increasing interest in new therapeutic tools, such as ECT, that can provide local control of disease and associated symptoms with relatively few side effects.

Moreover, ECT can be used in patients with locally advanced primary cancer (for example skin malignancies) when all other treatment options are deemed unfeasible (Fig. 2), have already failed, or were refused by the patient. Another possible application of ECT is with a neoadjuvant role as cytoreductive therapy [6]. Moreover, it can be performed as a palliative treatment in patients with locoregional recurrences or metastases. The aims of treatment in this case are control of symptoms, improve the quality of life, reduce new cancer related symptoms, and prolong overall survival [7,8].

## Contraindications

According to the European Standard Operating Procedures of Electrochemotherapy guidelines [9], ECT should not be recommended in patients with highly symptomatic and quickly progressive non-cutaneous lesions, due to low expectancies and ethical reasons. Moreover, patients who have had allergic reactions to bleomycin or cisplatin should not undergo the corresponding therapy. Furthermore, patients who have already been subjected to a cumulative dose of bleomycin > 400,000 IU should not be treated with ECT.

## Safety

The most commonly reported side effect of ECT is pain. A study from seven cancer centres in the International Network for Sharing Practices on Electrochemotherapy (INSPECT) [10] demonstrated that a high pain score before ECT is related to an increased pain score after ECT. Moreover, previous treatments with radiotherapy are related to a higher pain score after treatment with ECT. Larger skin lesions has been related to higher post-treatment pain [10]. The European Research on Electrochemotherapy in Head and Neck Cancer (EURECA) prospective study on 105 patients affected by skin cancer of the head and neck region reported only one major adverse event. A patient with a large, ulcerated lesion died because of a septic shock 2 days after ECT, despite antibiotic treatment and best supportive care. In case of full thickness lesions of the cheek, tumour necrosis with loss of oral competence and salivary fistula have been observed [11]. Other minor side effects reported in the literature are swelling, hyperpigmentation, maculo-papular rash, ulceration, and odour.

Overall, ECT in the oral cavity, oropharynx and hypopharynx is considered to be safe, with rare cases of bleeding. Swelling of the mucosa in this region can be dangerous if not expected and handled appropriately, for example with preventive tracheostomy [11].

## Outcomes

In the palliative setting (Fig. 2), ECT has been demonstrated to be effective in reducing bleeding, pain, suppuration, and need of medical care. Various features can influence the success of treatment, such as lesion's histology, dimension, site, and previous (chemo)radiotherapy. ECT is effective especially for small (less than 3 cm), non-ulcerated skin lesions, showing low toxicity, function preservation, improved quality of life, and good cosmetic results (Fig. 3). Regarding histology, ECT is more beneficial in BCC than in SCC and melanoma. When it comes to tumour size, it has been demonstrated to be inversely proportional to the

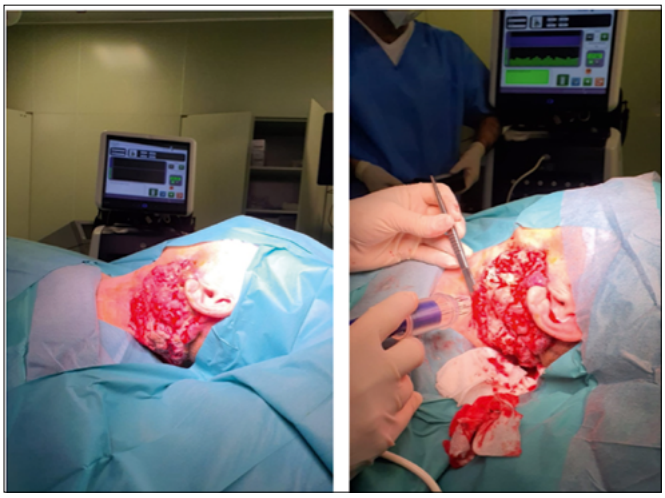


**Figure 2.** ECT as palliative treatment to reduce bleeding, pain and suppuration in regional recurrence of a parotid gland tumour.

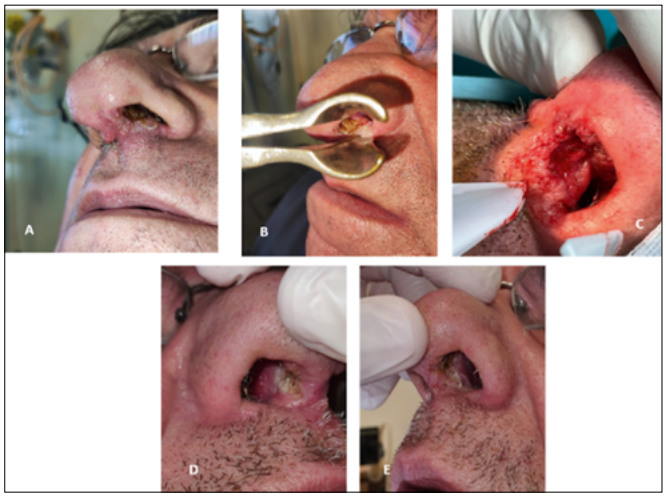


**Figure 3.** Local control with organ preservation by ECT in a patient affected by SCC of the columella and upper lip with pulmonary metastasis. **A** and **B**: pre-treatment evaluation; **C**: treatment by ECT; **D** and **E**: post-treatment evaluation.

efficacy of ECT. In particular, Bertino et al. [11] demonstrated that smaller lesions (< 3 cm) had better response, ECT was more successful in primary tumours than recurrences or metastases, and pre-treated lesions had worse responses than naïve ones. Specifically, lesions with a diameter ≤ 3 cm had an overall response rate of 88% *vs* 68% in those with a diameter > 3 cm. This feature can be related to lower blood supply and increased interstitial pressure in larger tumours, which may lead to inadequate exposure to chemotherapeutic drugs, and higher difficulty in covering the entire tumour volume by the electric field generated.

Moreover, several studies have shown that ECT is more effective in non-ulcerated lesions than in ulcerated ones. More specifically, for small tumours (< 3 cm) the difference in response rate in ulcerated versus non-ulcerated lesions was not statistically significant. In larger malignancies, non-ulcerated tumours showed better responses to ECT than ulcerated ones [13-16].

EURECA group reported positive results of ECT performed in patients with primary, recurrent, or metastatic skin cancers of the head and neck, which were not suitable for other standard therapeutic approaches. After one year of follow-up, overall disease-free survival was 89% (87% for SCC, 100% for BCC, and 89% for melanoma) [17].

In another series, ECT was shown to be beneficial in maintaining airway patency in peristomal recurrences [18].

It is interesting to note that, for recurrent lesions, a history of previous (chemo)radiotherapy affects more the possibility of reaching a complete response by ECT than previous surgical treatments [12].

Another European collaborative study [12], which enrolled 43 patients with mucosal recurrences of head and neck tumours for whom no further curative or palliative treatment was feasible, showed an overall response rate of 56%. In 7% of patients, a long-term complete response was observed with no evidence of recurrence.

Regarding quality of life, many studies have reported significant improvement in wellness perception as measured by the EuroQoL 5-dimensions questionnaire, and an important increase in physical and role functioning, with a decrease in pain and fatigue as quantified by the European Organization for Research and Treatment of Cancer core 30 quality-of-life questionnaire. Moreover, the analysis by the EORTC 35-question head and neck cancer-specific module demonstrated an improvement in all domains, in particular regarding the perception of feeling ill, pain, need for pain medication, and mouth opening [11].

## Conclusions

ECT is an effective and valid treatment strategy in patients with locally advanced head and neck cancers, when all other treatment options are unfeasible, have already failed, or have been refused by the patient. Moreover, ECT can have a neoadjuvant role in terms of cytoreduction, as well as a palliative use in patients with locoregional recurrences or metastases in which salvage surgery, second-line chemotherapy, immunotherapy or re-irradiation have been contraindicated by an accurate multidisciplinary evaluation, or for control of symptoms like bleeding, pain, and suppuration, thus reducing the amount of medical care needed and the expected rapid loss of function.

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The authors declare no conflict of interest.


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### *Author contributions*

FC, SD, PG, FB, CR: substantial contributions to the work reported in this manuscript; FC: design of the work, final approval of the version to be published; VdR: substantial contributions to the work reported in this manuscript, final approval of the version to be published; VP; FP, MB: final approval of the version to be published.

### *Ethical consideration*

No ethic committee aproval was required due to the nature of narrative review and no involvement of patients.

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