ELECTROCHEMOTHERAPY OF HEAD AND NECK CANCER

Giulia Bertino

University of Pavia, Department of Otolaryngology Head Neck Cancer, IRCCS Policlinico San Matteo Foundation, P.le Golgi 2, 27100 Pavia - Italy

E-mail:giulia.bertino@tin.it

Abstract: Electrochemotherapy (ECT) of head and neck cancer can be particularly tricky because the Otolaryngologist has to be able to manage many different pathological conditions: small or large cutaneous nodules located on the skin of the upper or lower face; subcutaneous or deep seated tumors in proximity of vital structures and small or large mucosal lesions of the oral cavity or the oropharynx. Each of these situations requires specific treatment modalities ranging from procedures that can be conducted under local anesthesia with the use of the standard fixed-geometry electrodes, to procedures that require general anesthesia, prophylactic tracheotomy and electroporation with the variable geometry.

The success of ECT in the head and neck area is strictly related to the capability of complete electroporation of the tumor nodules. The higher percentages of objective response are obtained in the skin areas, where the possibilities of complete coverage of the tumor mass is easier; while areas that cannot be easily exposed and reached with the electrodes, such as the oropharynx, or deep seated tumors show lower but still encouraging percentages of objective response. The development of new electrodes and the improvement of the procedures will increase the effectiveness of ECT in these peculiar conditions.

CURRENT PERSPECTIVES

Electrochemotherapy (ECT) is currently reserved to the palliative local treatment of cutaneous, subcutaneous or deep seated tumors of any kind of histology nor suitable to for standard treatments, the pain relief of tumor masses or the control of bleeding lesions (1). These pathological conditions can be particularly devastating in the head and neck area, where the standard treatments employed can add disabilities and worsen the residual quality of life in these patients (2).

Previous studies have proven the effectiveness of ECT in melanoma and non-melanoma skin cancers, with percentages of objective response verging 100% in basal cell carcinomas (BCC) and with healing of the treated lesions without damage of the surrounding tissues and minimal or nil impact on the aesthetic and function of the head and neck subsites (3).

The treatment of the oral and oropharyngeal lesions is more complex and depends on the capability to cover with the electric field all the tumoral bed. Thus, small lesions located in easily attainable areas such as oral cheek, floor of the mouth, internal lip, mobile tongue can be successfully treated with standard or finger electrodes; while larger nodules with complex tridimensional growth or located in the tongue base or oropharynx cannot be totally covered with the fixed geometry electrodes (2).

Despite these technical difficulties the percentages of objective response are encouraging (56% in the EURECA study) (4) and will be further improved with the development of new electrodes capable to completely electroporate tumors located in these particular areas or with the use of the single electrodes and the variable geometry (2).

The application of the variable geometry is particularly indicated for the treatment of head and neck deep seated tumors. These lesions are not simply hidden under the mucosal or skin visible surface, but they can be also located near vital structures (large blood vessels, cranial nerves), bone structures or in limited spaces. The

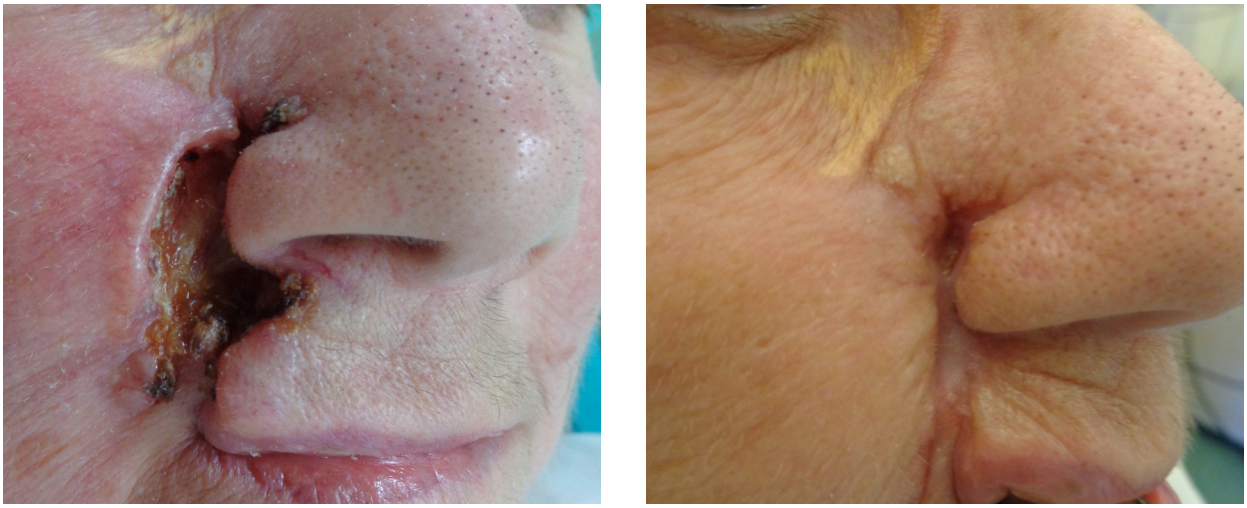

Figure 1 Primary BCC (left) and the response 6 months after 2 cycles of ECT (right)

determination of the adequate position for each single electrode and the sequence of the electric pulses deliverance during the procedure can be planned with specific softwares and Navigation Systems (5).

TREATMENT MODALITIES

Even if ECT in head and neck can be applied to the treatment of any kind of tumor site (cutaneous, subcutaneous, mucosal or deep seated) the choice of drug delivery, type of anesthesia and type of electrodes depend on the number, size, location and patient's general condition (Table 1) (2).

In general, when the tumors are located in the upper face or scalp, and are few (< 3 cm)and less than 2 cm in size, the procedure can be conducted under local anesthesia, both drugs (bleomycin or cisplatin) can be used according to the Standard Operating Procedures (SOP) (1), and the choice of the electrode depending on the nodules' morphology and thickness or depth of invasion; while in case of more than 3 nodules and larger than 2 cm it is better to proceed under general anesthesia and with bleomycin given intravenously.

In case of tumors located in the lower face or neck, intraoral or deep seated the procedure must be performed under general anesthesia because of the possibility of severe pain and muscle contractions; the choice of drug administration and type of electrodes follow the SOPs (1).

Moreover, in case of intraoral or oropharyngeal lesions, a profilactic

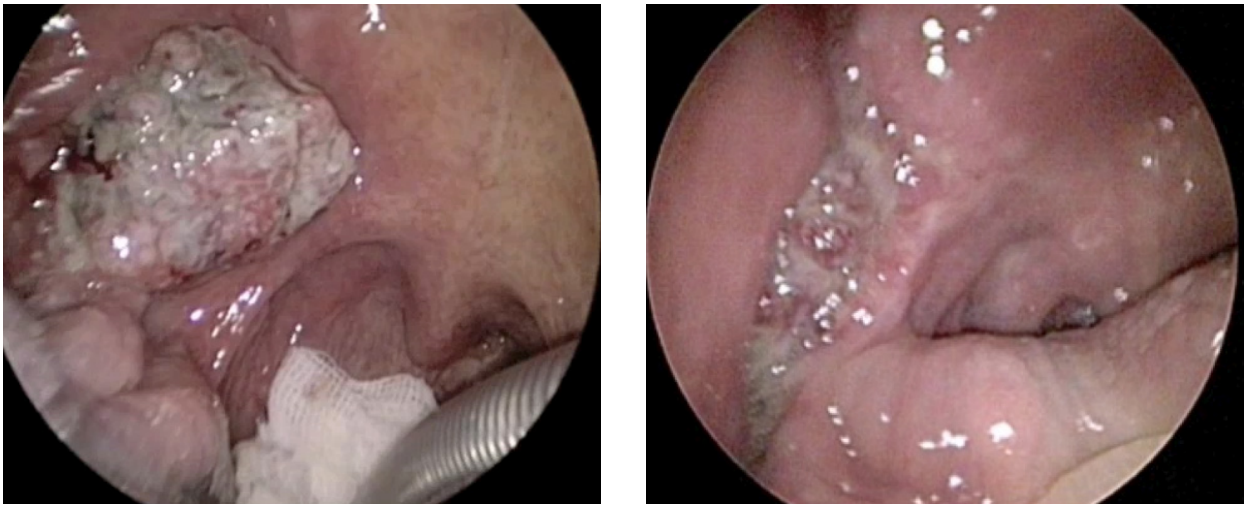

Figure 2 Primary SCC (left) and the response 2 months after ECT (right)

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

Treatment	Site, Number, Size	Anesthesia	Drug administration	Electrode
Modality A	Head, face < 3 nodules < 2 cm	Local ± Sedation	Bleomycin i.t./i.v. Cisplatin i.t.	Plate (if superficial) Row needle, Hexagonal, Finger (if deep
Modality B	Head, face > 3 nodules > 2 cm	General	Bleomycin i.v.	Row needle, Hexagonal
Modality C	Cheek, Chin, Neck, Intraoral, Deep seated Any number Any size	General	Bleomycin i.t./i.v. Cisplatin i.t.	Row needle, Hexagonal, Finger Variable geometry

tracheotomy has to be considered due to the risk of swelling of the soft tissues.

CONTRAINDICATIONS

Contraindications to ECT in head and neck are the same of the SOPs (1) with the adjunct of macroscopic infiltration of the internal jugular vein or carotid artery because of the risk of blowout secondary to tumor necrosis induced by ECT (Table 2).

Moreover, attention must be paid in the treatment of full-thickness lesions of the cheek or peristomal recurrences because of the risk of salivary fistulas, or in the treatment of full-thickness lesions of the lip for the risk of labial incompetence (2,6).

FUTURE PERSPECTIVES

Usually, ECT is a safe treatment in head

Table 2 Absolute and relative contraindication 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, Peristomal lesions		High risk of salivary 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

and neck cancer patients because it results in minimal or null aesthetic and functional compromise and leads to healing of treated tumor lesions without damage to the surrounding healthy tissues. Therefore, particular attention must be reserved to elderly patients because the risk of severe side effects and necrosis can be higher due to increased serum levels of bleomycin, induced by the reduction of total body water and a decline in glomerular filtration rate (7). In order to avoid these possible complications, some authors have already proposed a reduced dose of bleomycin (10.000 IU/m^2) in elderly patients, instead of the standard dose of 15.000 IU/m^2, since the serum clearance curve of bleomycin is slower (less than 500 ml/min) in elderly population (7).

The effectiveness of ECT in the treatment of cutaneous and subcutaneous tumor nodules, is high, with reported percentages of objective response approaching 100% (3); for this reason a future role for ECT as a first-line treatment of head and neck cancer, particularly in elderly patients, or as neo-adjuvant treatment for those cases in which surgical procedures and/or radiotherapy would be too devastating in achieving proper oncological results can be considered, even if randomized clinical trials are still necessary to confirm this possibility.

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 (8).

The combination of ECT and immunotherapy may have a long-term effect on local and systemic cancer eradication and seems to be a future perspective (9,10).

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). Thus, 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 (8).

Alternatively, immune stimulation through electrogenetherapy (EGT) has also raised great hope for the treatment of cancer. Sersa et al. 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 (11).

REFERENCES

1. Gehl J, Sersa G, Wichmann Matthiessen L, Muir T, Soden D, Occhini A, et al. Updated standard operating procedures for electrochemotherapy of cutaneous tumours and skin metastases. Acta Oncologica 2018;25:1-9.
2. Benazzo M, Bertino G, Groselj A. Electrochemotherapy of Head and Neck Cancer. In Miklavčič D. ed. Handbook of Electroporation, Springer; 2017. p.1-14.
3. Bertino G, Sersa G, De Terlizzi F, Occhini A, Plaschke CC, Groselj A, et al. European research on electrochemotherapy in head and neck cancer (EURECA) project: results of the treatment of skin cancer. Eur J Cancer 2016;63:41-52.
4. Plaschke CC, Bertino G, McCaul JA, Grau JJ, de Bree R, Sersa G, et al. European Research on Electrochemotherapy in Head and Neck Cancer (EURECA) project: Results from the treatment of mucosal cancers. Eur J Cancer 2017;87:172-181.
5. Groselj A, Kos B, Cemazar M, Urbancic J, Kragelj G, Bosnjak M, et al. Coupling treatment planning with navigation system: a new technological approach in treatment of head

and neck tumors by electrochemotherapy. Biomed Eng Online 2015;14(Suppl 3):S2.

6. Campana LG, Bertino G, Rossi CR, Occhini A, Rossi M, Valpione S, et al. The value of electrochemotherapy in the treatment of peristomal tumors. Eur J Surg Oncol. 2014;40(3):260-262.
7. Groselj A, Krzan M, Kosjek T, Bosnjak M, Sersa G, Cemazar M. Bleomycin pharmacokinetics of bolus bleomycin dose in elderly cancer patients treated with electrochemotherapy. Cancer Chemother Pharmacol 2016;77:939–947.
8. Calvet CY, Mir LM The promising alliance of anti-cancer electrochemotherapy with immunotherapy. Cancer Metastasis Rev 2016;35:165-177.
9. Brizio M, Fava P, Astrua C, Cavaliere G, Savoia P. Complete regression of melanoma skin metastases after electrochemotherapy plus ipilimumab treatment: an unusual clinical presentation. Eur J Dermatol 2015;25:271–272.
10. Mozzillo N, Simeone E, Benedetto L, Curvietto M, Giannarelli D, Gentilcore G, et al. Assessing a novel immuno-oncology-based combination therapy: ipilimumab plus electrochemotherapy. Oncoimmunology 2015;4(6):1-8.
11. Sersa G, Teissie J, Cemazar M, Signori E, Kamensek U, Marshall G, et al. Electrochemotherapy of tumors as in situ vaccination boosted by immunogene electrotransfer. Cancer Immunol Immunother 2015;64:1315–1327.