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Electrochemotherapy as palliative treatment in patients with advanced head and neck tumours: Outcome analysis in 93 patients treated in a single institution

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ABSTRACT

Purpose: To describe outcomes of Electrochemotherapy as palliative treatment in patients with advanced head and neck (H&N) tumours.
Methods: Ninety-three patients (120 treatment sessions) with H&N recurrent and/or metastatic neoplasm were treated. Treatment response was assessed 4 weeks after ECT with clinical examination and two months after the first evaluation with a CT scan of the H&N for deep lesions evaluation. The grade of bleeding and pain before, at the end of treatment and one week after ECT were evaluated.
Results: Five percent of complete responses, 40% of partial responses were registered. Disease progression was seen in 20% of patients after the first ECT procedure, the remaining 34% of patients experienced stable disease. A good control of pain and bleeding was obtained, especially in patients with moderate symptoms before the treatment. No toxicities related to ECT were seen.
Conclusions: ECT is an interesting antitumoral therapy in advanced chemo and radio-refractory H&N neoplasms. ECT is able to reduce frequent symptoms, such as pain and bleeding, improving quality of life without damage to healthy tissue and with limited side effects. Moreover, ECT reduces hospitalization time and may contribute to an overall reduction in healthcare costs associated with advanced H&N cancers care.

Introduction background

Carcinomas of the head and neck (HNC) account for more than 5% of all malignancies worldwide, and in 90% of cases are squamous cell carcinomas (SCC) [1]. Despite aggressive, site-specific multimodality therapy, a significant proportion of patients will develop disease recurrence, with up to 60% risk of local failure and up to 30% risk of distant failure [2,3]. A number of different malignancies, other than HNC, can occur in the head and neck region, among which melanoma and cutaneous carcinoma, and, especially in an advanced phase, when becoming chemo and radio-resistant, they will lead to poor prognosis and grim quality of life of the affected patients. These tumours (HNC and other malignancies arising from head and neck regions) are particularly challenging to treat and patients are eventually candidate for palliation [4,5]. According to Head and Neck 2015 NCCN guidelines, patients with unresectable or persistent disease the patients are treated with reirradiation ± systemic therapy, systemic therapy, clinical trial or best supportive care [6], depending on the patient's performance status (PS), preference and the life expectancy.

Electrochemotherapy (ECT) is an antitumour strategy, which couples electroporation and concomitant delivering of antineoplastic drugs. Electroporation consists in application of short-intensity pulsed electric fields to tumour cells, in response to which, the plasma membranes permeability to different hydrophilic drugs, transiently increases, facilitating cellular uptake of cytotoxic agents [7–10].

Intravenous antineoplastic drugs seldom reach sufficient doses in

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the tumour cells, often due to an irregular vascolarization, a wide fibrosis and/or several necrosis areas present in the tumour mass. This last phenomenon is particularly frequent in tumor tissues yet treated with several chemotherapy lines and, mainly, with radiation therapy.

ECT avails of electroporation to allow increased uptake of chemotherapeutic drugs directly into tumour cells. In addition to a direct antitumor function of the drug, ECT has several mechanisms of action, and they may involve vascular and immunologic phenomenon's. The vascular effect commonly referred to as "vascular lock" support ECT ability to quickly and effectively control bleeding lesions [10–15].

Finally, ECT is able to indirectly activate immune response against different tumour antigens. Tumour cells destruction, during ECT, leads to several immunogenic antigen exposure, which can recruit antigen presenting cells (APC) from peripheral blood. These last are capable to elicit a robust immune response against tumour. Data inherent this immunologic mechanisms of ECT have been reported in clinical studies enrolling patients affected by advanced melanoma [16,20].

Potentially, every kind of malignancy of head and neck may be suitable for ECT, but in clinical practice, it was often employed for treating cutaneous carcinoma and subcutaneous metastases. Subcutaneous metastases are a very common feature in patients with advanced melanoma, and they are not easy to face. ECT may be considered as a good alternative to further chemotherapy lines, or in alternative, it could be coupled with chemotherapy in patients whose disease is mainly a cutaneous disease.

The effectiveness of Electrochemotherapy has been demonstrated in a large variety of tumors predominantly for the treatment of cutaneous tumors using electrodes with fixed geometry [21,22]. In a recent meta-analysis on 44 prospective studies comparing five skin-directed therapies (ECT, radiation, photodynamic therapy, intralesional therapy, and topical therapy), ECT demonstrated an OR rate of 75.4% (CR rate, 47.5%) with a low toxicity profile (grade 3 in less than 6% of patients). In this analysis, melanoma comprised 83.3% of all cutaneous metastases [23].

Many clinical reports described results of electrochemotherapy in treatment of H&N tumours [24–27]. ECT results in a minimal or nil function impact and leads to healing of treated tumor lesions without damage to the healthy tissues. For these reasons, ECT is described as an alternative to palliative chemo or radiotherapy and partial and complete remission rates have been reported in various clinical trials with low frequency of side effects [24,28]. Electrochemotherapy can be applied to mucosal head and neck recurrent tumours accessible to the procedure with promising objective response, survival and toxicity profile. With the aim of assessing the outcome of palliative ECT treatment in patients with advanced head and neck tumours at our Institution, National Cancer Institute of Naples, we treated from May 2011 to April 2017, 93 patients with diagnosis of advanced late stage head and neck carcinoma, according to Standard Operating Procedure established in ESOPE study [29,30].

The aim of this prospective study was to evaluate the efficacy of ECT in term of Disease Control Rate (DCR) (CR + PR + SD) in the palliative setting in patients with H&N recurrent and/or metastatic neoplasm. The secondary end points were evaluation of Pain (VAS score) and effect of ECT on bleeding.

Methods

Patients characteristics

Between May 2011 and April 2017, ninety-three patients (56 male and 37 female, with a median age of 74 years [range 21–92]) were recruited in the Maxillo facial and Head & neck Department of Istituto Nazionale Tumori of Naples. Patients were included in our study if they had diagnosis of recurrent and/or metastatic neoplasm of the head and neck, treated with at least two chemotherapy lines and/or with radiation therapy on the head and neck region. Eighteen patients were treated for two times and 3 of them for four times, for a total of 120 sessions of Electrochemotherapy.

Institutional ethics committee approved the clinical trial and a multidisciplinary tumour board agreed on ECT indication for each patient. Pre-, intra-, and post ECT outcomes were stored in an electronic database and retrospectively collected. Each patient signed a written informed consent to participate to the study.

Table 1 reports histological characteristics and tumor size. Table 2 reports pain information before and after treatment. Table 3 report bleeding information before and after treatment.

Table 1
Histotype, bleeding and pain characteristic of H&N cancer patients.

Characteristics	N°	%
Patients gender		
Male	56	60.2
Female	37	39.7
Age		
Median 74 yrs (range 21–92)		
Histotype		
Oropharyngeal and oral cavity ca	17	18.3
Neck metastasis	24	25.8
Laryngeal carcinoma	7	7.5
Carcinoma from salivary glands	7	7.5
Skin		
Squamous cell carcinoma	15	16.1
Basal cell carcinoma	19	20.4
Other	4	4.3
Tumor size		
< 3 cm	55	59.1
> 3 cm	38	40.9

Surgery and ECT protocol

The technical procedure and patient selection were performed according the ESOPE guidelines [29,30]. Inclusion criteria were life expectancy longer than 3 months; measurable cutaneous or mucosal tumor lesions. Eligible were all patients affected by recurrent, metastatic, or primary cancer of the H&N area not suitable for surgery or chemo/radiotherapy on the basis of poor general condition, age, cardiac deficit not related to electrical malfunction, reduced lung performance, comorbidities, high risk of major intra-postoperative complications, risk of anesthesia, previous treatments, and when the surgery would be too demolitive to be resolutive. Exclusion criteria included clinically manifested arrhythmia, interstitial lung fibrosis, epilepsy, an active infection, a known allergy to bleomycin, kidney failure, previous treatment with bleomycin at the maximum cumulative dosage, and different anticancer therapies administered within 2 weeks of ECT. All patients were treated under general anesthesia and a specific pain management protocol was employed, consisting in intravenous infusion of fentanyl at dose of 2 μg/kg and intravenous paracetamol at dose of 1000 mg, both administered 30 min before the start of electric pulses. ECT was performed on target lesions, administering bleomycin intravenously (15.000 IU/m^2) before the application of electrical pulses to the target area. Electric pulses were applied by needle electrodes

Table 2
Pain information before and after treatment.

	VAS before treatment N. (%)	VAS post treatment N. (%)	p value*
VAS < 3	30 (32.2%)	48 (51.6%)	0.00002
3 ≤ VAS < 7	38 (40.9%)	42 (45.2%)	
VAS ≥ 7	25 (26.9%)	3 (3.2%)	

* Chi square test.

Table 3
Bleeding information before and after treatment.

Bleeding	Bleeding before treatment N. (%)	Bleeding post treatment N. (%)	p value*
Moderate	31 (33.4%)	22 (23.7%)	0.00012
Severe	23 (24.7%)	6 (6.4%)	
No	39 (41.9%)	65 (69.9%)	

* Chi square test.

with linear (n = 16), hexagonal configuration (n = 90) or finger electrodes (n = 14) (IGEA S.p.A., Carpi, Italy) depending on the size and localization of the tumors.

In this study, generally linear needle electrodes were used to approach cutaneous, lymph node and subcutaneous lesions smaller than 3 cm, hexagonal needle electrodes were employed in wider tumours. Finger electrodes were used to reach less accessible lesions, such as those localized in the oropharynx (tonsil and base of tongue).

Cliniporator™ (IGEA S.p.A., Italy) was used to deliver electric voltage with the following parameters: 8–96 pulses of 400–730 V and 910–1000 V/cm, of 100 µs duration, at 5000 Hz repetition frequency according to ESOPE (European Standard Operating procedure of Electrochemotherapy) protocol and its update [29,30].

The surgeon performed multiple insertions (20 on average, range 1–105) of the electrode in the tumor tissue covering the complete area of the lesion to be treated and possibly a margin area of free tissue growths of 3–5 mm (overtreatment) around the lesion itself. Treatment was completed within the window from 8 to 40 min after the end of the Bleomycin bolus. This time window ensures the maximum concentration of drug within the lesion.

After ECT procedure, a 24-hours infusion pump containing morphine, ketorolac, omeprazole and metoclopramide was administered to each patient, with the aim to reduce pain induced by needle implant.

Treatment response assessment

Treatment response was assessed 4 weeks after ECT with clinical examination and two months after the first evaluation with a CT scan (Computed Tomography) of the head and neck for evaluation of deep lesions (especially in oral cavity, lymph nodes and oropharyngeal masses). RECIST 1.1 (response evaluation criteria in solid tumors) criteria were employed for the response assessment.

Because our secondary endpoint was the pain control, all the patients were carefully evaluated with the aim to measure initial grade of pain. The VAS (visual analogue scale) was employed to grade the pain at the start, the end of treatment, one week after the ECT and at each follow-up visit.

The other secondary endpoint of the study was the bleeding control. Bleeding was considered moderate when it slows or stops with pressure and the blood may soak a few bandages, but it is not fast or out of control. Generally, patients need medical assistance regularly (no more than once a week). It was defined severe when it does not stop or slow down with pressure, blood is pumping from the wound and quickly soaking through bandage after bandaging and medical assistance is requested at least twice a week.

Statistical analysis

Quantitative variables were expressed with median, mean, and range. All categorical data values were expressed as absolute numbers and percentages. Chi square test was performed to emphasize statistically significant difference between percentage values in different population subgroups. Kruskal Wallis non-parametric test for continuous variables was performed to emphasize statistically significant differences between median values in different population subgroups.

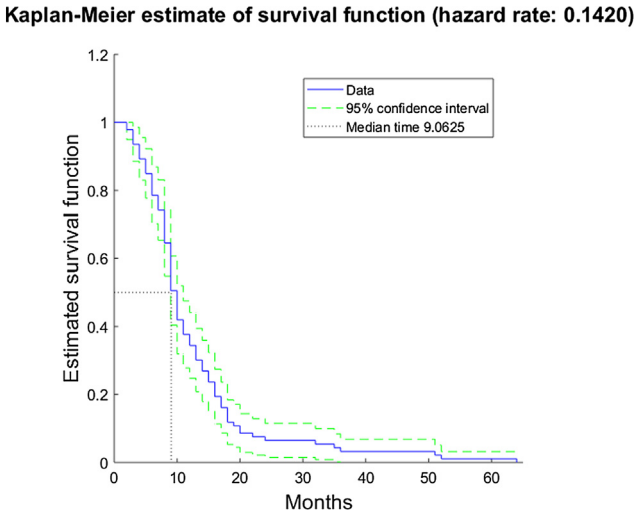

Fig. 1. Kaplan-Meier estimate of Overall survival function. Time 0 is the time of ECT treatment.

Survival estimate was calculated with Kaplan-Meier test.

P value < 0.05 was considered significant for all tests. All analyses were performed using Statistics Toolbox of Matlab R2007a (The MathWorks Inc., Natick, MA).

Results

At a median follow up of 14 months (range 2–64), 28 (30%) patients were alive and the remaining 65 (70%) died for disease progression. The median overall survival time was 9,1 months (Fig. 1). Complete responses (CR) were seen in 5 (5%) cases, and 37 (40%) partial responses (PR) were registered at 2 months. Progressive disease (PD) was seen in 19 (20%) patients after the first ECT procedure, the remaining 32 (34%) patients experienced a stable disease (SD).

Tumour size significantly influenced the response to ECT, with higher overall response (OR) rate in 30 (54.5%) of patients whose lesion was smaller than 3 cm (p value = 0.007). In the group of patients with lesion > 3 cm OR was observed in 10 patients (26.3%). The cutoff was selected at 3 cm on the bases of previous clinical experiences [31]. Best response for target lesions by patient, based on maximal percentage of tumor reduction is shown in Fig. 2.

Pain was well controlled in 28 out of 30 patients (93.3%) with initially low grade pain (VAS < 3), in 36 out of 38 (94.7%) with moderate grade (VAS ≥ 3 but < 7), and 23 out of 25 (92%) with severe pain (VAS ≥ 7) at diagnosis. Pain evaluation using the VAS scale showed significant pain reduction after ECT. Median VAS score before treatment was 6.02 vs. 2 at 1 month after ECT (p value at Kruskal Wallis test < 0.001, see Fig. 3). Bleeding was well controlled in 27 out 31 patients with initially moderate symptom and in all 23 patients with severe bleeding at diagnosis.

Pain and bleeding control, on the other hand, was not related to VAS values and bleeding status before treatment (p value at Chi square test = 0.91 and 0.07, respectively).

No toxicities related to ECT were seen except for slight edema in the site of electrode implant, which disappeared one week after the procedure.

Fig. 4 is shown a case of basal cell carcinoma of nasal root and internal canthus of left eye treated with ECT. The lesion disappeared 6 weeks after the treatment.

A patient with large high-grade leyomiosarcoma with involvement of the nose and the left nasolabial fold treated was treated with ECT of the residual lesion after surgical debulking. Three months after ECT even if a large defect of the nasal tip was present a good skin healing of the left alar wall and nasolabial fold was obtained (Figs. 5–7).

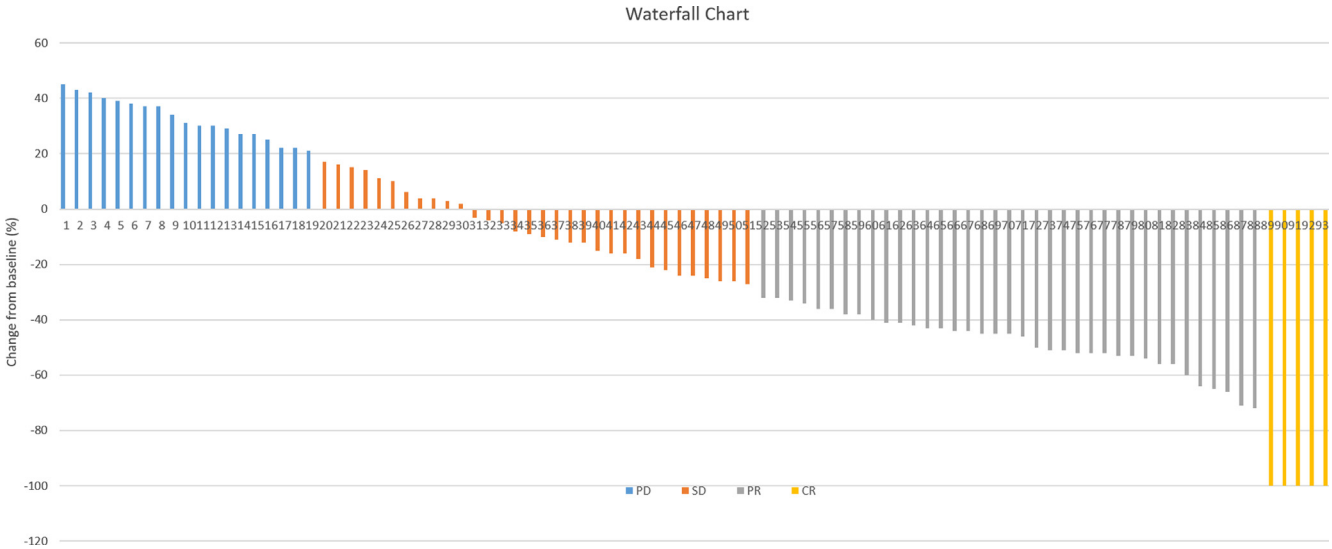

Fig. 2. Best response for target lesions by patient, based on maximal percentage of tumor reduction. RECIST = Response Evaluation Criteria in Solid Tumors.

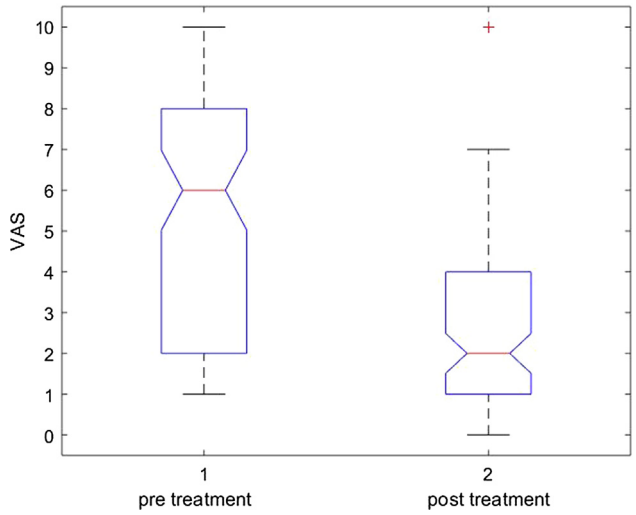

Fig. 3. Box plot of VAS value before and after treatment.

In Figure 8 a case of SCC of the nose is shown. The lesion was resolved at 8 months and at 36 months no disease was present and a good skin healing was obtained.

The patients provided written informed consent to publishing their photos.

Discussion

The head and neck area is a particularly complex anatomical region, due to the presence of critical structures, such as carotid and cranial nerves, compacted in a small space. Thus, tumours arising in the head and neck are difficult to manage. Some of them recur locoregionally, at distant sites only or both, after a multimodality treatment and become chemo and radio-refractory diseases. Recurrent disease is particularly challenging to treat. In fact, only few patients with locoregional recurrence can be salvaged by surgery or reirradiation while most patients with recurrent or metastatic disease only qualify for palliative treatment. In these circumstances local and systemic treatment are mainly directed at ameliorating symptoms, improving quality of life and possibly prolonging the overall survival [32,1]. In recent years, ECT use in treatment of the tumours in the H&N area has increased mainly because ECT, in addition to good local tumor control, results in minimal function impairment and leads to healing of treated tumor lesions without damage to the healthy tissues. These characteristics compare favorably to other available treatment options, such as radical salvage surgery in terms of toxicity profile, functional and aesthetics outcomes. Several clinical trials described ECT as a valid alternative to palliative chemo or radiotherapy and partial and complete remission rates have been reported with low frequency of side effects [24–26]. The use of ECT not limited to palliative treatment, but as definitive treatment in patients with inoperable head and neck cancer, especially in elderly patients was also suggested [1].

As demonstrated by Bertino et al. in a recent clinical trial on skin cancer of the H&N better responses are obtained with small lesions (≤ 3 cm), primary and naïve tumours. Tumour size in all the tumours (BCC and all other histologies) significantly affected the response to electrochemotherapy. In more detail, tumours < 3 cm in diameter showed OR of 88%, whereas for tumours > 3 cm in diameter OR was 68%. Previous surgery least affected the outcome compared to (chemo) radiotherapy or multiple treatments of recurrent tumour nodules [31]. Electrochemotherapy is well tolerated and does led to a significant improvement of quality of life at 1-year follow-up, in patients with primary or recurrent skin cancer of the H&N area with an overall and disease-free survival of 76% and 89% respectively described [31]. In a prospective trial of six European institutions, ECT was investigated on 36 patients with recurrent and mucosal head and neck tumours. An objective response of 56% was observed with complete response 8 (19%), partial response 16 (37%), stable disease 10 (23%), progressive disease 3 (7%), and not evaluable 6 (14%). Three patients (7%) remained in complete response at 30, 34, and 84 months post-treatment. The treatment procedure was generally well-tolerated [31]. These favourable results indicate that electrochemotherapy could play a role in patients with recurrent head and neck cancer [33]. Treatment with ECT of inoperable basal cell carcinomas and squamous cell carcinomas localized in the head of elderly patient should be always considered [34].

Di Monta et al. in their retrospective, single-center study confirmed that ECT is more effective than other therapeutic options in locally advanced SCC treatment, they showed a OR after ECT treatment of stage III SCC of 81% and CR of 22.7% [35]. Pichi et al. in a study on 24 patients with recurrent H&N tumors showed that ECT treatment is generally well accepted by the patients and can be repeated without worsening quality of life of the patients while effectively managing symptoms. Even in case of partial response, ECT resulted in a sensible improvement of pain, bleeding reduction, and need for medical/paramedical care. The reduced need for the medical support, reducing

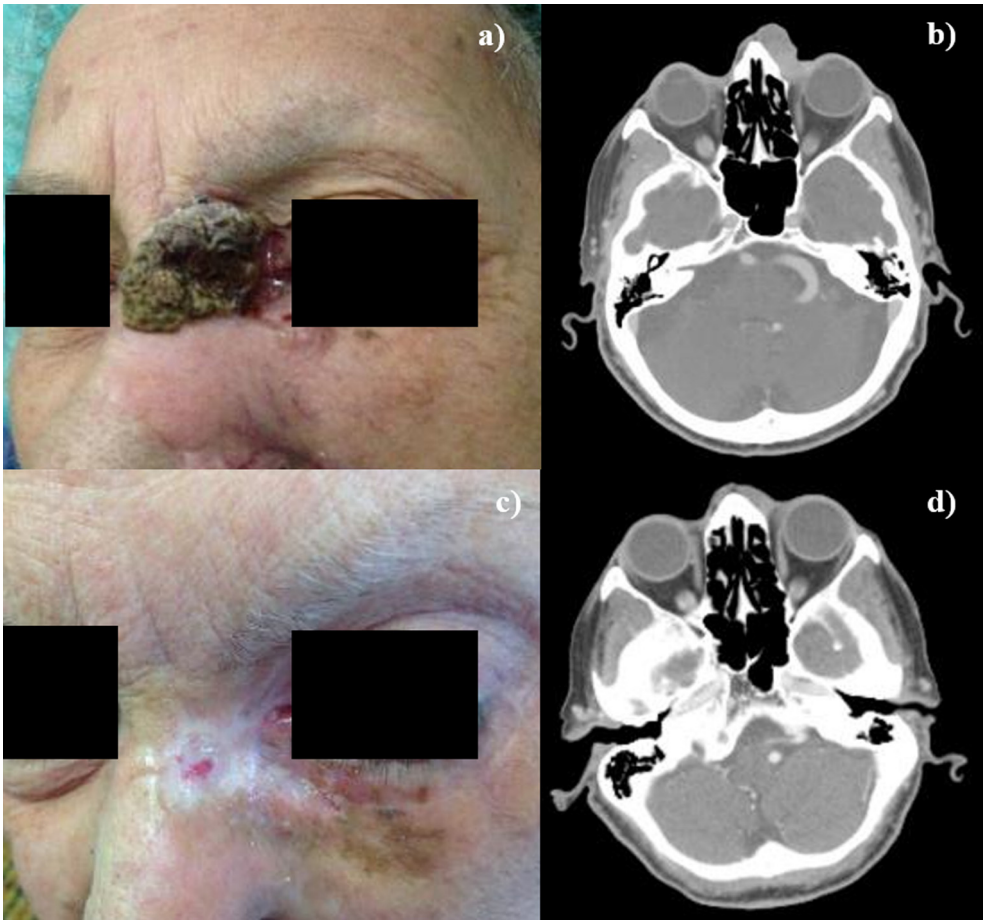

Fig. 4. Basal cell carcinoma of nasal root and internal canthus of left eye. CT scan: the lesion involves the skin and the medial aspect of the orbit (a); Six weeks after ECT: the lesion disappeared with good healing of the skin (b); Six weeks after ECT: CT scan shows evident reduction of previous lesion (c).

hospital travel even if in presence of minor percentage of complete response represent an advantage for patients from the psychological point of view and at the same time reduces costs for the hospital in terms of the commitment of medical and nursing personnel [36].

In our study, we have observed an OR of 45% with a 5% of CR.

Our results showed a lesser percentage of CR in comparison to the literature, probably due to the assumption that all the patients had a chemo and radio-refractory disease, having experienced at least two chemotherapy lines in addition to radiation therapy. Another possible explanation is the heterogeneity of the treated diseases, in fact most of them were HNC, but our casuistic comprised also, primitive skin cancers and one case of soft tissue tumor. As already showed by Bertino et al [31] lesion with size lesser than 3 cm showed better results in term of Overall response. Our results are in accordance to this observation and lesser OR could be explained with the evidence that 38 out 93 patients (41%) had lesions larger than 3 cm, which is recognized as a factor related to poor outcome.

Importantly, our main endpoints were the pain and bleeding control and in the study, we have observed a 94% and 93% of pain and bleeding control, respectively. Knowing the risk factors predictive of post-operative pain (pre-operative pain, previous irradiation, large tumor size and high current values), antalgic treatment can be better planned in advance [37]. Tumour size in all the tumours significantly affected the response to electrochemotherapy. In more detail, tumours < 3 cm in diameter showed OR of 88%, whereas for tumours > 3 cm in diameter OR was 68%. In our study, peri-operative pain control was achieved using a specific pain management protocol, consisting in a continuous intravenous therapy administered after the ECT procedure.

In line with the literature, we have registered a significantly poorer response rate in patients bearing lesions larger than 3 cm, while, the site of the primitive tumour did not affect the outcome. No major complication were observed and patients not required long hospitalization. No toxicities related to ECT were seen except for slight edema in the site of electrode implant, which disappeared one week after the procedure. A more robust system for the evaluation of the clinical course with particular reference to the quality of life would be appropriate (EORTC and Q5DL-5 questionnaires) in future studies.

Although ECT as palliative treatment is a well-established option for patients in advanced stage of illness, the curative potential of ECT in the treatment of head and neck cancer either alone or in combination with other therapies has to be investigated in patients with early stage of H&N tumors as suggested by Landstrom et al. [38]. The Authors carried out a phase II trial enrolling 19 patients with early stage (T1-2) oral and base of tongue carcinomas and treated them with upfront ECT with curative intent, followed by adjuvant radiation therapy. They observed no recurrence during the entire follow-up period and all the patients were alive at 5 years and reported only mild local toxicity [38].

A limitation of our study is patient heterogeneity in terms of clinical features including both mucosal and skin carcinomas. The present study indicate that electrochemotherapy is possible to perform also on mucosal head and neck tumors in palliative setting without serious side effect. Nevertheless, systematic data collection and detailed tumor description including localization, stage (TNM), and histology, and administration of specific questionnaires to evaluate quality of life would be desirable. The lack of a control arms to not allow to draw any definitive conclusion on the benefit of the intervention. For this reason, a new randomized two arms study is ongoing and a control receiving

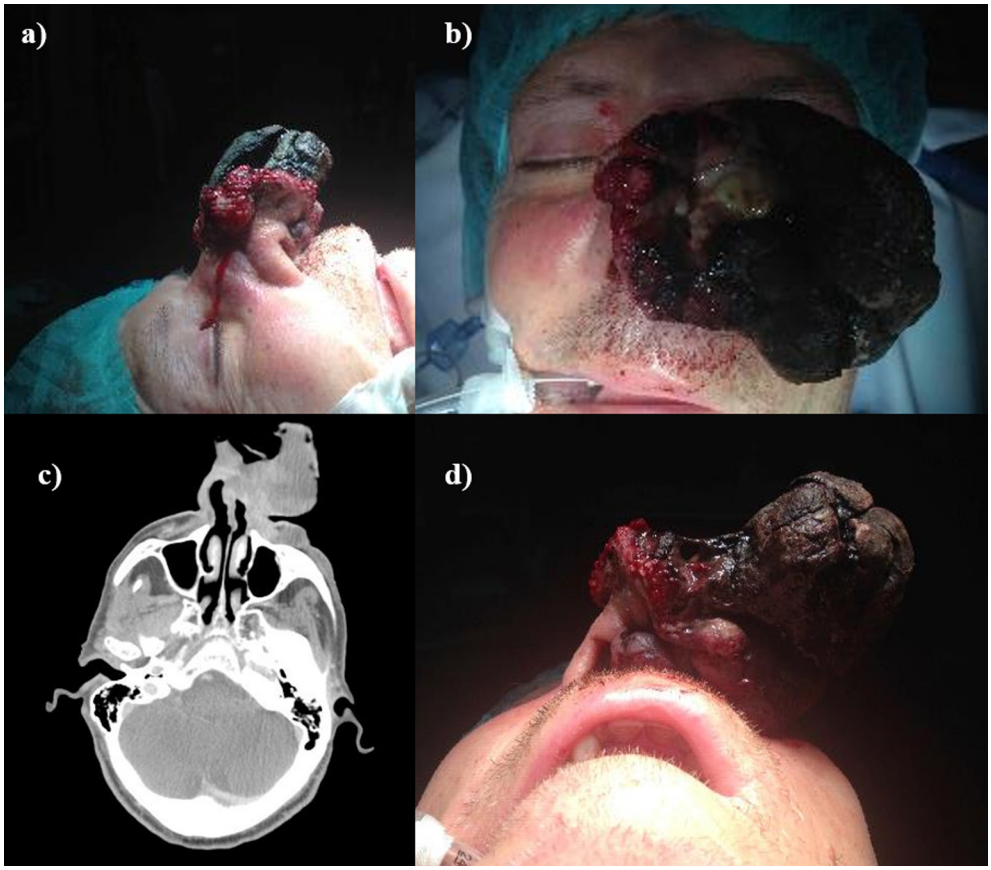

Fig. 5. Patient with Large high-grade leyomiosarcoma (a, b, d), CT scan: the tumour involves the nose and the left nasolabial fold (c).

conventional systemic therapy is included.

Conclusion

In conclusion, ECT is an interesting antitumoral therapy that may have a role not only in skin and subcutaneous tumours, but also in advanced chemo and radio-refractory neoplasms of H&N. The treatment is possible to perform across the mucosa showing that ECT is able to reduce frequent symptoms, such as pain and bleeding without damage to healthy tissue and with limited side effects. ECT reduces hospitalization time and may contribute to a reduction in healthcare costs associated with advanced H&N cancers care. This determines an improving of quality of life in term of psychological and practice point of view. An early treatment of tumor with size ≤ 3 cm would be

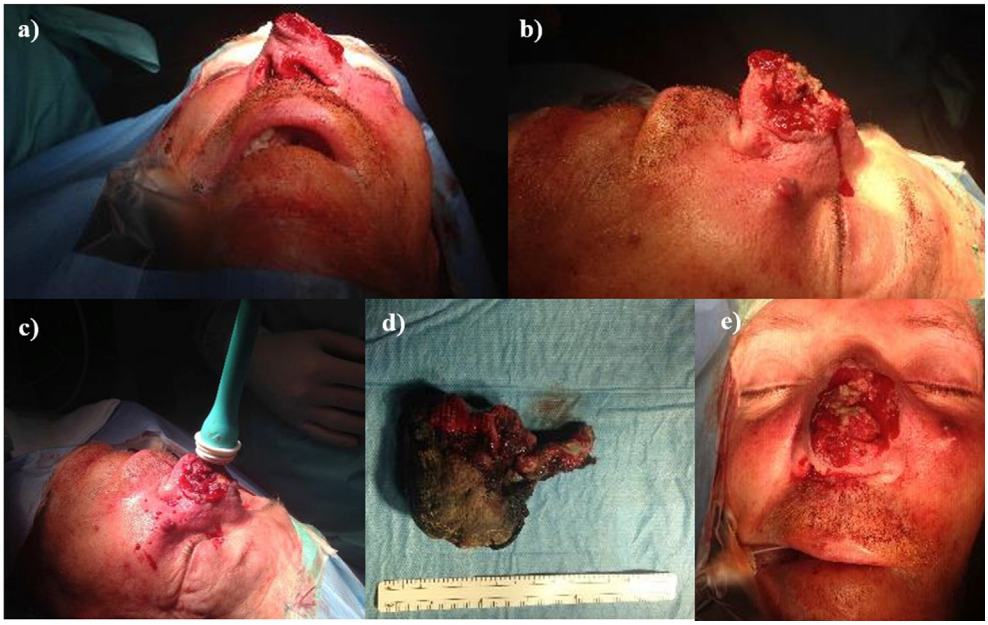

Fig. 6. Intraoperative imagines of patient showed in Fig. 3 (a, b, e); Electrochemotherapy of the residual lesion after surgical debulking (c); Surgical specimen (d).

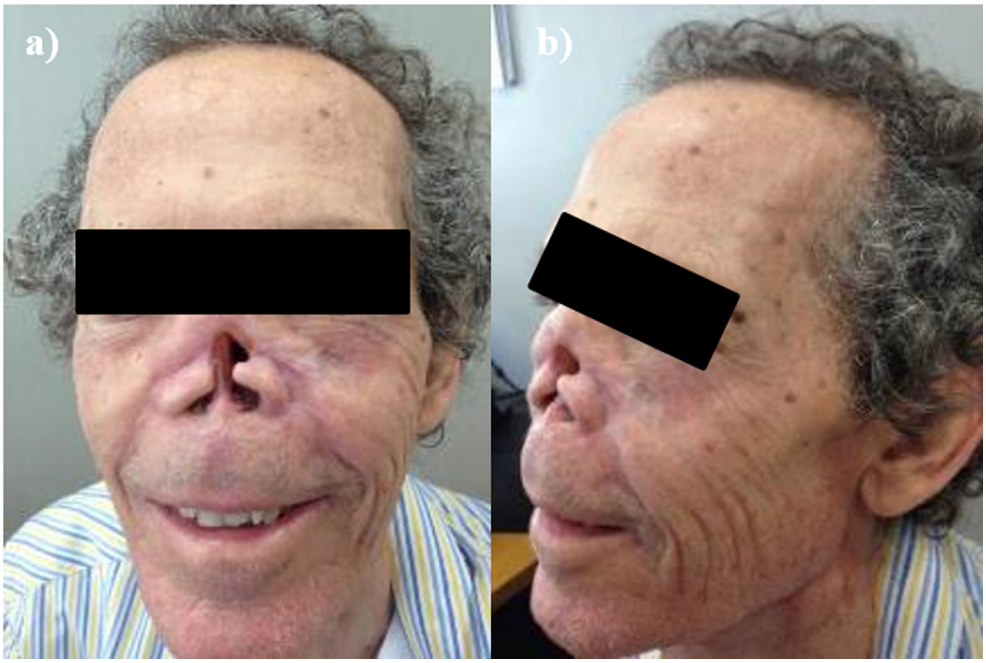

Fig. 7. Patient with Large high-grade leyomiosarcoma of the nose three months after ECT: large defect of the nasal tip with good skin healing of the left alar wall and nasolabial fold (a, b).

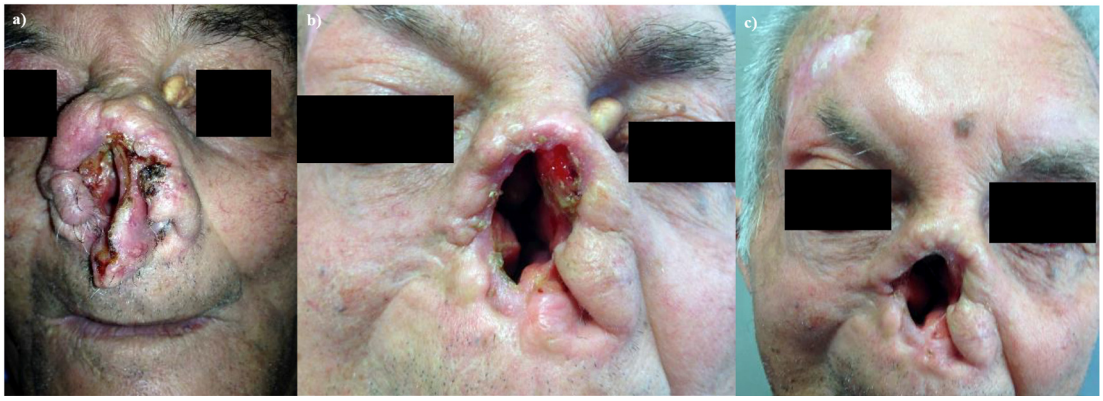

Fig. 8. Patient with SCC of the nose: before ECT (a), 8 months and 36 months after ECT treatment (b, c).

desirable to obtain a better local control of the disease.

Conflict of interest and financial disclosures

Authors declare no conflict of interest. Authors exclude any relevant financial activities outside the submitted work.

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