

Electrochemotherapy in plastic surgery

New perspectives from the pandemic experience in the treatment of advanced skin cancers in elderly and frail patients

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Background: During the COVID-19 pandemic, most of the surgical units involved in the treatment of skin cancers could continue their activities, but the reevaluation of cases and the adaptation of the surgical approach, to limit access and hospital stays, proved to be mandatory. The study aims to demonstrate how the electrochemotherapy (ECT) approach guarantees a chance to keep on delivering comprehensive oncologic surgical treatment in a difficult and high-risk cohort of patients.

Methods: We collected 35 elderly and frail patients affected by advanced and metastatic skin cancer who were unsuitable for a standard surgical approach. They were submitted to an ECT protocol, while evaluating the impact of ECT on health-related quality of life, using the EuroQoL-five dimensions-three levels (EQ-5D-3L) instrument at baseline and after treatment.

Results: A general improvement in health status was reported from the preoperative (mean 56.9) to the postoperative period (mean 63.7), according to the EuroQoL-visual analog scale measure. The EuroQoL-five dimensions descriptive system showed a reduction of the “patients reporting problems” from the baseline, in the domains for self-care (–27%), usual activities (–24%), pain/discomfort (–43%), and anxiety/depression (–11%).

Conclusions: Rapid intervention, minimum hospitalization, palliation in selected cases, and postoperative management with telemedicine may represent the only option in the hands of a surgeon to treat advanced oncologic lesions in fragile patients, especially in a pandemic scenario. ECT can be considered a safe and effective procedure, well tolerated by most elderly and “high-risk” patients.

Keywords: Electrochemotherapy; Skin cancer; SARS-CoV-2 pandemic; Cutaneous metastases; EQ-5D-3L questionnaire; Elderly; Fragile patients

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Introduction

It has been over 4 years since the 2019 declaration of the COVID-19 pandemic, and most of the world has been facing new variants of the SARS-CoV-2 virus and new waves of COVID-19 cases.¹

The health measures arranged during the first wave have been implemented to ensure maximum hospital availability for the diagnosis and treatment of patients affected by COVID-19.

On the other hand, because of the reorganization of health care, it was mandatory to establish a standard of care for chronic and cancer patients, too.

The Italian Association of Medical Oncology and several other physician organizations have recommended evaluating the possibility of postponing definitive local therapy for patients with cancer.²

The situation required a careful comparison of the early risks of COVID-19 infection versus the later risks of skin cancer progression.^{3,4}

The treatment of cutaneous and subcutaneous tumors, regardless of their histological origin, usually requires a surgical approach, which is considered to be the most effective when applicable.^{5,6}

Nonetheless, it was mandatory to consider the risks associated with surgical demolition, those connected to anesthesia, and a prolonged intraoperative surgical time.⁷

Moreover, in the case of elderly patients affected with important comorbidities, any surgical treatment may require inpatient

hospital care, which may be burdened by a prolonged stay. This could be related to the potential exposure to contagion and hospital isolation, as caregivers were not allowed access to most surgical departments during the SARS-CoV-2 pandemic.

In this regard, albeit with great sacrifice and suffering, we have treasured the dramatic pandemic experience and bitter teachings. We present an alternative therapeutic approach based on the well-demonstrated efficacy of electrochemotherapy (ECT) on skin tumors,^{8,9} exploiting its characteristics of intervention rapidity and low morbidity, especially towards a cohort of fragile, elderly patients, who were considered at greater risk in the COVID-19 era.

ECT can target tumor cells and tumor blood flow by combining the cytotoxic effect of bleomycin or cisplatin and the local application of short electric pulses, which allow the delivery of a high concentration of drug selectively into the tumor cells through transient electroporation of membranes. The antivasculature mechanism is expressed in two ways: vasoconstriction and endothelial damage. The first facilitates the entrapment of the drug in the tumor tissue, whereas the second involves immediate and irreparable damage to the intratumoral circulation. Therefore, this method proved useful either for vascular neoplasms or hemorrhagic ones.^{10,11}

Consequently, it represents a palliation tool for the inoperable elderly patient, where the management of the bleeding would represent the main care goal.¹²

Our plastic surgery unit, being part of a national center for the diagnosis and treatment of patients with cancer, continued its activity uninterrupted during the pandemic. Examinations were performed daily, and a load of elderly patients ended up taking up most of the operating list.

Our commitment during this difficult period also consisted of maintaining and delivering appropriate care for those patients who, due to age, comorbidities, and the clinical status of skin cancer, required prompt treatment with low surgical impact and a short period of hospitalization. In such a scenario, ECT may be considered a safe and effective method, especially in a selected cohort of “high-risk” patients. Moreover, few studies have evaluated the impact of ECT on health-related quality of life (HRQOL), most of them focusing on the cost-effectiveness of the treatment. The increase in the technique’s use and the affirmed antitumor efficacy have highlighted the need to deepen the evaluation in terms of quality of life, especially when the treatment is targeted at frail elders with primary cancer.¹³

We prospectively evaluated HRQOL using the EuroQol-five dimensions-three levels (EQ-5D-3L) instrument, a validated patient-reported measure of health status developed to provide a simple and standardized measure of health for clinical and economic assessment.^{14,15}

Materials and methods

We collected a cohort of patients treated with ECT during a period from February 2020 to February 2021. All of them underwent a preoperative multidisciplinary evaluation at the disease management team and received collegial indication for electrochemotherapy treatment.

Our study has been performed with respect to the ethical principles of the Declaration of Helsinki, and all patients provided written informed consent.

HRQOL was estimated by collecting EQ-5D-3L questionnaires at baseline and after a complete or partial response following the treatment.

The system investigates five different aspects of health: mobility (from “no problems in walking about” to “confined to bed”); self-care (from “no problems with self-care” to “unable to wash or dress myself”); usual activities (from “no problems with performing my usual activities” to “unable to perform my usual activities”); pain/discomfort (from “no pain or discomfort” to

“extreme pain or discomfort”); anxiety/depression (from “not anxious or depressed” to “extremely anxious or depressed”). Each dimension generates three different levels (1–3): no problems, some problems, and extreme problems.

The descriptive system comprises the EQ-5D visual analog scale (EQ-VAS) which records the respondent’s self-rated health on a vertical VAS where the endpoints are labeled “The best health you can imagine” and “The worst health you can imagine.” The pre- and post-treatment results of both assessment systems were compared individually, and the results were analyzed using a t-test after normality checking with the Shapiro-Wilk test. A *P* value of less than 0.05 was considered statistically significant.

Inclusion criteria for ECT were represented by patients with cutaneous and/or subcutaneous primary tumors or metastases, either confirmed histologically or without a histological diagnosis. Exclusion criteria included allergy or sensitivity to bleomycin; pulmonary fibrosis; previous exposure to cumulative bleomycin dose of 250,000 IU/m²; and current pregnancy or lactation.

Patients were introduced to prehospitalization, which includes an anesthetic risk assessment and routine blood tests: hepatic and renal function, blood count, coagulation tests, viral markers blood test for hepatitis B and C and electrocardiogram analysis. Given the need to limit the attendance of fragile patients within the hospital structure, the above procedures, including the pulmonary function tests when indicated, were all performed on the same day. The basic radiological evaluation of the chest and the lung diffusion capacity test were useful to evaluate any changes that may derive from pulmonary toxicity associated with the used drugs, such as bleomycin.

Subsequently, patients scheduled for surgery were screened for SARS-CoV-2 through an oropharyngeal molecular swab. Only patients who tested negative for SARS-CoV-2 were admitted to the ward and underwent treatment, performed either as a daycare surgery or as a fast-track inpatient. All treatments were conducted through the Cliniporator electroporator device (IGEA S.p.A.) with intravenous administration of bleomycin at a dosage of 15,000 IU/m² per body surface. According to the European Standard Operating Procedures on Electrochemotherapy standardized criteria and their updated SOPs,^{13,16} the electrical impulses were transmitted 8 minutes after completing the drug infusion, allowing adequate body distribution. The impulses were delivered, when necessary, for a maximum of 40 minutes to guarantee the ideal systemic concentration of the drug. Two types of needle electrodes were used: linear and hexagonal, the latter used for larger diameter lesions (>1 cm).

Results

During the first pandemic year, 35 patients were treated, four of whom required a reduction in the bleomycin dose because of impaired renal function. The mean age was 70 years (range, 41–90).

Table 1 describes the demographic characteristics of the patients.

Twenty patients (57%) had received at least one systemic treatment for metastatic disease, among them, six (17%) melanoma patients were on active treatment with immune checkpoint inhibitors. In 25 (71.4%) of 35 patients, the treatment was administered under target-controlled infusions propofol sedation (0.8–1.5 mcg/ml) and local anesthesia (lidocaine 2%), whereas 10 (28.5%) patients were treated with locoregional anesthesia only. The mean duration of the treatment, including any sedation and anesthesia procedure, was 15 minutes, with an average of 75 transmitted impulses. (range 11–160). Intravenous paracetamol was sufficient for postoperative pain control. The average hospital stay was 2 days. No significant

Table 1.
Demographic features of patients

Characteristic	
Patients included, n (%)	35 (100)
Sex, n (%)	
Male	23 (66)
Female	12 (34)
Age, years, median (range)	70 (41–90)
Comorbidity, n (%)	
Diabetes	6 (17)
Cardiovascular disease	12 (34)
Hypertension	11 (31)
APT/OAC	17 (49)
HIV/HCV	3 (9)
Kidney failure	4 (11)
Hematological disease	4 (11)
Follow-up, n (mo)	6
Histotype, n (%)	
Melanoma	18 (51)
Angiosarcoma	2 (6)
Basal cell carcinoma	2 (6)
Squamous cell carcinoma	6 (17)
Kaposi sarcoma	5 (14)
Breast cancer	1 (3)
Renal cell carcinoma	1 (3)
Undifferentiated sarcoma	1 (3)
Buschke- Lowenstein tumor	1 (3)
Disease presentation, n (%)	
Primary	12 (34)
Recurrent/metastatic	23 (66)
Multiple face carcinomas	2 (6)
Lesions per patient, n (%)	
Multiple	28
Single	7
ECT cycles, n (%)	
1	31 (89)
2	4 (11)
Retreatment reason (n = 4), n %	
Partial response	2 (6)
Recurrence after complete response	1 (3)
New Lesions outside treated area	1 (3)

Table 2.
Tumor response to ECT according to histotype

Response	Melanoma	NMSC	CKS	BC	Angiosarcoma	RCC	Sarcoma
	(n = 18) n (%)	(n = 8) n (%)	(n = 5) n (%)	(n = 1) n (%)	(n = 1) n (%)	(n = 1) n (%)	(n = 1) n (%)
CR	12	6	4	0	1	1	0
PR	6	2	1	0	1	0	1
PD	0	0	0	1	0	0	0

BC indicates breast cancer; CKS classical Kaposi sarcoma; CR, complete response; NMSC, nonmelanoma skin cancer; PD, progressive disease; PR, partial response; RCC, renal cell carcinoma.

adverse events were reported during or after the procedure. The distribution of tumor response according to the different histotypes is presented in Table 2. All patients answered each of the five dimensions comprising the EQ-5D descriptive system and the EQ-VAS measure. Table 3 and Figure 1 indicate detailed patient-reported outcomes.

Significant reductions of the “patients reporting problems” from the baseline, were found in the domains of self-care (–27%), usual activities (–24%), pain/discomfort (–43%), and anxiety/depression (–11%). The measure for “mobility” increased in the number of patients with problems, but this was not observed to be statistically significant.

The EQ-VAS (Figure 1.)-generated data confirmed the improvement in the health status. From the preoperative (mean

56.9) to the postoperative period (mean 63.7), the variation was statistically significant ($P < 0,05$). The mean follow-up was 6 months.

Postsurgical management was organized based on the restrictions applied to outpatient hospital access. The appointments were spaced by at least 30 minutes to ensure the correct amount of space between patients, especially in the waiting rooms, and, when possible, the follow-up was conducted entirely with telemedicine.¹⁷ Patients were already instructed on medication procedures and healing times upon discharge. Patients could be followed completely safely thanks to telematics consultations, and a doctor could be available every day according to the patient’s needs.

Discussion

Multiple studies demonstrate that ECT represents a reliable method active on various tumor entities. Born as an eminently palliative treatment, it finds space as a curative therapeutic procedure, especially in primary skin neoplasms.^{18,19}

The surgical treatment of skin tumors may require a more or less complex reconstruction, which can occur in several stages, and in the COVID-19 era, most secondary reconstructive procedures have been postponed, compromising the patient’s quality of life.^{20–22} ECT reduces the need for challenging soft-tissue reconstructions, guaranteeing the delivery of a proper oncologic treatment through a low-risk procedure with short hospitalization and high effectiveness in selected cases^{23–25} (Figure 2).

The SARS-CoV-2 pandemic highlighted that the aging population represents one of the most important public health issues of the twenty-first century. The elderly represent the concept of frailty: the decision-making process is turned into a real therapeutic challenge because of the elder’s unpredictable response to standard treatments. The augmented risk of age-associated functional, physiological, and cognitive changes may increase the incidence of medical and surgical complications.^{7,26,27}

As reported in recent literature, many institutions tried to preserve routine cancer treatment with different approaches and efficacy.^{22,23}

Often, the difficulties linked to the choice of a surgical option in the elderly and frail patients are also burdened by advanced-stage diseases, sometimes occupying multiple or large areas of the body (Figures 3 and 4).

Our protocol offered an alternative but effective therapeutic approach in a pandemic scenario, which can be repurposed nowadays as a standard for selected high-risk patients. It allows broadening therapeutic opportunities for skin cancer pathology while preventing patients’ exposure to infectious risks, limiting the waiting lists, and the eventual complications related to longer hospitalization.²⁸

Rapid intervention, low morbidity, and high efficacy rate in fragile patients best represent the target of our protocol. The rapidity of intervention and reduced morbidity respond to the need to reduce surgical steps and hospitalization, minimizing associated complications.²⁹

Standard applications of ECT limit the operating time in a range (depending on the number and size of the lesions) that shall not exceed the limit of 40 minutes for the application of an effective impulse. Moreover, the procedure needs to be performed under sedation combined with local anesthesia or under regional anesthesia, which probably represents its main advantage.

Strøm et al,⁷ presented a review highlighting the dysfunctions, especially cognitive, related to general anesthesia. Cerebral aging, linked to cerebrovascular problems and neuronal degeneration, makes the elderly patient particularly vulnerable to the negative effects of anesthesia and slows down recovery from surgical stress. Therefore, a “low-invasive” surgical treatment that reduces the time spent in the operating room and the risks

Table 3.

The EQ-5D 3L is a simple, descriptive questionnaire to evaluate health-related quality of life. The table shows data and proportions reporting levels within EQ-5D dimensions, pre- and post-ECT treatment

	Mobility		Self-care		Usual activities		Pain/discomfort		Anxiety/depression	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Level 1	13 (37.1%)	12 (34.2%)	24 (68.5%)	27 (77.1%)	6 (17.1%)	13 (37.1%)	7 (20%)	19 (54.2%)	8 (22.8%)	11 (31.4%)
Level 2	22 (62.8%)	23 (65.7%)	7 (20%)	8 (22.8%)	25 (71.4%)	22 (62.8%)	18 (51.4%)	13 (37.1%)	18 (51.4%)	16 (45.7%)
Level 3	0 (0%)	0 (0%)	4 (11.4%)	0 (0%)	4 (11.4%)	0 (0%)	10 (28.5%)	3 (8.5%)	9 (25.7%)	8 (22.8%)
Total	35 (100%)	35 (100%)	35 (100%)	35 (100%)	35 (100%)	35 (100%)	35 (100%)	35 (100%)	35 (100%)	35 (100%)
n. reporting some problems	22 (62.8%)	23 (65.7%)	11 (31.4%)	8 (22.8%)	29 (82.8%)	22 (62.8%)	28 (80%)	16 (45.7%)	27 (77.1%)	24 (68.5%)
Change in n. reporting problems		+1		-3		-7		-12		-3
% change reporting problems		+4%		-27%		-24%		-43%		-11%

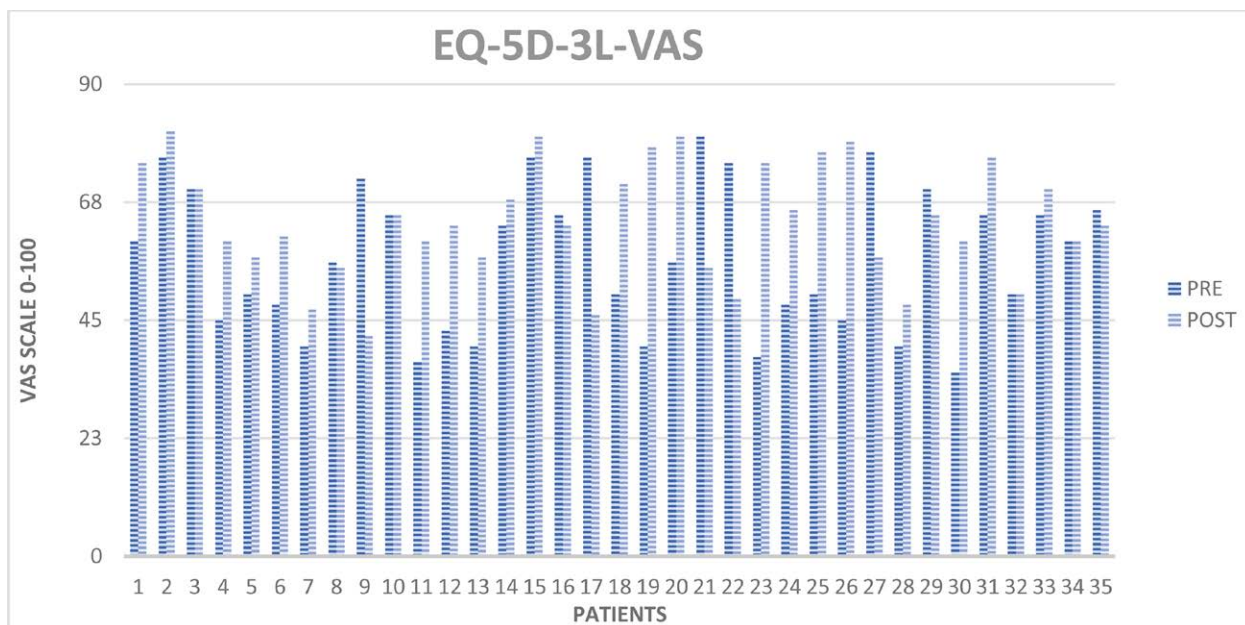


Figure 1. The EQ-VAS (0–100) evaluating the overall health status. A comparison of the data during the preoperative phase and after the last postoperative follow-up. EQ-VAS indicates EuroQol–visual analog scale.

associated with anesthesia can represent the best therapeutic alternative for such a selected cohort of patients. The efficacy constitutes the other key component of our treatment protocol. The literature available on the subject shows high efficacy rates in terms of objective response and complete response, ranging from 60% to 80% after a single treatment.¹³

In a recent article, Sersa et al.³⁰ confirmed ECT as a valid and safe alternative to surgical resection in the oldest-old patients, supporting it even for primary skin cancer. No significant deviation was documented in terms of results, compared with the younger population’s counterpart.

We can legitimately establish that the procedure falls by law into the category of localized destructive techniques to treat skin neoplasms. Along with these, it could share reduced rates of relapse and low morbidity, although there are no comparative studies to date.⁹ Primary radiotherapy is a potential alternative, although its effectiveness is considered lower than that of surgery. Even if performed in a hypofractionated scheme, it requires weekly treatments (and high patient adherence to the protocol due to the need for repeated hospital visits), increasing risks and potential contagion.^{31,32}

Recently, an increase in patients with advanced-stage tumors was registered.³³

Whether this might depend on the delay induced by the restrictions related to containment measures for the SARS-CoV-2 infection, which may have caused an expansion of

waiting lists, or on a greater aggressiveness of the disease in the elderly population, remains unclear. In any case, these conditions would have required complex surgical procedures, affecting the intra- and postoperative morbidity and mortality for both anesthetic and surgical reasons, such as bleeding, potential cardio-cerebrovascular events, and wound infections.³⁴ An ECT-dedicated pathway allowed us to treat patients that otherwise would have been rejected or delayed according to other protocols. We have been able to deliver prompt therapeutic procedures, especially in that cohort of patients considered at the highest risk during this critical period.

When considering older and complicated patients, curative treatment can be found in a palliative-type regimen. To “cure” can mean “willing to assist,” supporting and improving daily life. Palliation intended as a “cure,” which therefore goes beyond terminal care, represents one aim of ECT and sometimes one of the therapeutic goals of the procedure. In the literature, only a few authors discuss the palliative treatment of cutaneous neoplasms, and no technique is of choice.^{12,35,36}

Moreover, not much is known about the impact of this therapeutic technique on the quality of life. In our series of 35 patients, we reported preoperative and postoperative EQ-5D-3L health-related outcomes,^{14,37} highlighting satisfactory results (Table 3 and Figure 1). The most significant reduction results in the pain/discomfort dimension, evidence of how the method

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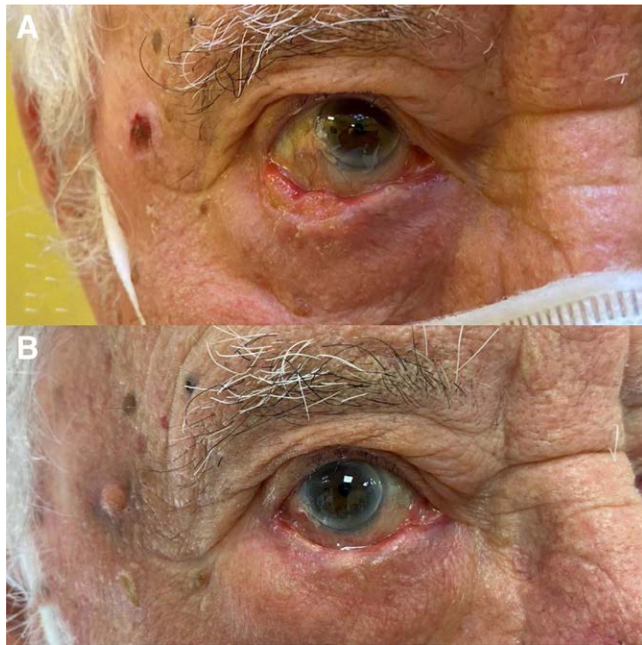


Figure 2. Elderly patient with multiple skin cancers of the face. Preoperative (A) and 6 weeks postoperative (B) view of infiltrating basal cell carcinoma of the lower eyelid treated with ECT. ECT indicates electrochemotherapy.



Figure 4. Palliative surgery in an elderly patient with severe comorbidities and organ metastases from an extended aggressive squamous cell carcinoma of the lower lip. Preoperative (A) and 4 weeks postoperative (B) view following ECT. ECT indicates electrochemotherapy.



Figure 3. Palliative intervention in a patient with melanoma metastases of the scalp during treatment with anti-PD-1 therapy. Preoperative (A) and 4 weeks postoperative (B) view following ECT. ECT indicates electrochemotherapy.

expresses the maximum potential in the local control of the pathology and its complications. The contextual evaluation according to the EQ-VAS (between 0 and 100) showed a significant increase in the overall health status with a preoperative mean of 56.9 (± 13.8 SD) and a postoperative mean of 63.7 (± 10.9 SD).

Clinical experience and clear scientific evidence highlight that wound dressing plays an important role in avoiding superinfection and speeding up healing, allowing the fragile patient to recover in the shortest time possible.³⁸

To limit hospital access for postoperative follow-up and medications, a telemedicine platform was activated, through which the treated patient is educated to take care of the wound and can communicate with an on-call doctor to manage any issue related to the treatment and follow-up.³⁹

Conclusion

The management of the elderly and frail surgical patients has always been a therapeutic challenge, demonstrated above all during the SARS-CoV-2 pandemic. ECT proved to be a safe and effective procedure that is well tolerated in this setting. Even nowadays, this technology may allow us to extend the catchment area and, at the same time, ensuring high therapeutic standards. As far as we know, this is the first report focusing on the impact of ECT on the HRQOL of a fragile population, using the EQ-5D-3L instrument.

Despite this, we still register a lack of controlled studies on the elective “low-impact” surgical method to treat cutaneous neoplasms in elderly patients.

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