

Electrochemotherapy Treatment for Squamous Cell Carcinoma of the Lip: A Case Report

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Background: Squamous cell carcinoma is a malignant tumor that affects the skin and mucous membranes. It may present as painless superficial lesions, or as rapidly growing, exophytic masses, sometimes ulcerated, which can invade and damage surrounding tissues. It is the second most common malignant neoplasm of the skin, characterized by high clinical variability, which makes early diagnosis and timely treatment essential to improve prognosis. The aim of this case report is to evaluate the clinical efficacy, tolerability, and durability of response of electrochemotherapy in the treatment of cutaneous squamous cell carcinoma of the lip in patient with compromised general health.

Case Presentation: We report the case of a 79-year-old male with multiple comorbidities, including chronic kidney disease, diabetes, and ischemic heart disease, who presented with a rapidly growing lesion on the lower lip. The surgical approach would entail a functional deficit of the lips and an aesthetic impairment. Due to the patient's systemic condition, a more conservative treatment was chosen, namely treating the neoplasm with electrochemotherapy.

Results: The treatment led to controlled necrosis of the lesion and complete healing by secondary intention within three months. The patient experienced no functional impairment or recurrence during a four-year follow-up.

Conclusion: This case highlights the potential of electrochemotherapy as a safe and effective alternative for managing lip squamous cell carcinoma, particularly in patients who are not candidates for surgery or radiotherapy. The favorable clinical and aesthetic outcomes support its consideration in selected cases.

Keywords: squamous cell carcinoma, lip cancer, intralesional, bleomycin, electrochemotherapy, non-melanoma skin cancer

Introduction

Squamous cell carcinoma (SCC) is a malignant tumor that affects the skin and mucous membranes. It may present as painless superficial lesions, or as rapidly growing, exophytic masses, sometimes ulcerated, which can invade and damage surrounding tissues. It is the second most common malignant neoplasm of the skin, characterized by high clinical variability, which makes early diagnosis and timely treatment essential to improve prognosis.^{1,2} In recent decades, there has been an increase in cases of SCC, primarily due to prolonged sun exposure and conditions of immunosuppression, such as in transplant patients. The tumor predominantly affects older individuals and males, reflecting the influence of cumulative environmental and lifestyle risk factors.^{3,4} The lower lip is one of the areas most exposed to solar radiation due to its prominent position on the face. In fact, SCC of the lip has long been considered a condition that predominantly affects the lower lip, due to its greater exposure to chronic sunlight and its strong association with tobacco use. These risk factors play a decisive role in the onset of precancerous lesions and their progression to malignancy, particularly in the lower lip, an area that is anatomically exposed and highly vulnerable.⁵ Squamous cell carcinoma of the lip accounts for approximately 20–30% of all oral cancers worldwide, with survival rates varying significantly depending on the timeliness of diagnosis. This type of tumor represents the vast majority of malignant neoplasms affecting the lip,

approximately 90–95%, with a clear predominance in the lower lip, likely due to its greater and more prolonged exposure to environmental factors such as ultraviolet radiation. In fact, its incidence varies according to geographic and demographic factors, reflecting differences in UV exposure, behavioral habits (such as smoking), and access to prevention and early diagnosis programs.⁶ Early detection allows for more effective treatment and reduces the risk of local invasion and metastasis, making therapy less invasive.⁷ Accurate staging is essential for the treatment of squamous cell carcinoma, actually, it is based on clinical and histopathological parameters such as tumor depth of invasion and the presence of lymph node metastases, which together significantly influence the prognosis and guide therapeutic decisions, including surgery, radiotherapy, or multimodal approaches.⁸ There is conflicting evidence regarding the prognostic value of tumor thickness, histological classification, and perineural invasion, while some studies support their inclusion in staging systems due to their potential predictive relevance, others question their accuracy and clinical utility. Further research is needed to clarify the role of these factors in guiding prognosis and therapeutic decisions. In fact, among the available treatment options are primary surgical excision, radiotherapy, brachytherapy, and emerging immunotherapies, reflecting the significant progress made over recent decades.

Given the clinical and social importance of the lips, effective management of lip squamous cell carcinoma is crucial, for survival rates exceed 80% in early-stage disease, but decline sharply in the presence of lymph node metastases or recurrence.⁹ In the early stages and in cases of localized disease, surgical excision represents the first-line treatment, ensuring high cure rates. However, the surgical approach requires lip reconstruction, often resulting in microstomia and functional impairment of the orbicularis oris muscle, along with aesthetic consequences in an area of high cosmetic relevance.¹⁰ Radiotherapy and brachytherapy are valid therapeutic alternatives, particularly in cases with positive surgical margins or when the tumor is deemed inoperable. For advanced or recurrent disease, chemotherapy and immunotherapy are emerging as promising systemic treatment options and are currently the focus of increasing clinical and scientific interest.¹¹ For patients who are not eligible for surgical intervention, several alternative therapies are available, particularly for early-stage or superficial lesions, these include laser treatments (CO₂, Nd:YAG), topical agents (such as imiquimod and podophyllin), photodynamic therapy, and thermochemotherapy.¹² Such approaches aim to preserve lip function and aesthetics, offering effective, minimally invasive options in selected clinical scenarios. In the late 1980s, a locoregional therapy was proposed that combines electroporation and chemotherapy to enhance drug uptake and cytotoxicity, providing a localized tissue action with negligible systemic effects. The aim of this case report is to evaluate the clinical efficacy, tolerability, and durability of response of electrochemotherapy in the treatment of cutaneous squamous cell carcinoma of the lip, particularly in patients who are not eligible for conventional treatments such as surgery or radiotherapy.

Case Report

A 79-year-old male patient with chronic kidney disease, diabetes, hypertension, and a history of ischemic heart disease one year prior presents with a rapidly growing exophytic lesion involving the right margin of the lower lip (**Figure 1**). The diagnosis of cutaneous squamous cell carcinoma was confirmed through histopathological analysis of tissue obtained via incisional biopsy.

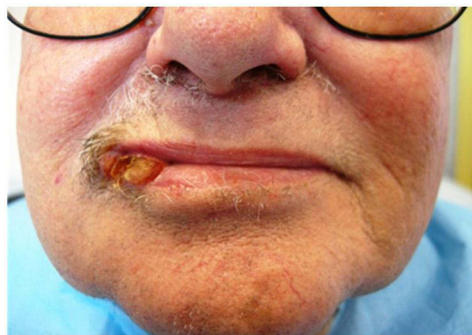


Figure 1 A patient with squamous cell carcinoma of the lip before treatment.

The patient was treated with ECT at the Department of Maxillo-facial Surgery, University of Tor Vergata, Rome in September 2019. The patient with a primary tumor had refused all standard therapeutic options.

Therapeutic decisions were made by a multidisciplinary board, following a thorough consultation involving the surgeon, radiation oncologist, medical oncologist, and the patient himself.

Prior to the electrochemotherapy procedure, conscious sedation was performed using intravenous midazolam and fentanyl followed by local anesthesia. The interested region was anesthetized using a 4% articaine solution (Curasept), delivered through targeted local infiltration and injected around the entire lesion to achieve complete regional desensitization. This approach provided effective pain control while minimizing systemic exposure to anesthetic agents, an important consideration given the presence of multiple comorbidities in the patient population. Articaine was selected due to its rapid onset of action, superior tissue diffusion, and favorable safety profile, making it particularly suitable for outpatient dermatologic procedures. The use of a localized anesthetic technique also facilitated precise electrode placement and optimal patient cooperation during the ECT session.¹³

After thorough disinfection of the surgical field and delineation of the lesion margins, intralesional injection of bleomycin was administered into the squamous cell carcinoma of the labial commissure, distributing the drug at multiple points to ensure uniform coverage of the tumor volume. Subsequently, the electroporation phase was performed by applying electric pulses using a multi-needle electrode over the entire surface of the lesion and approximately 1 cm of the surrounding healthy tissue, taking care to avoid overlapping applications. The entire procedure was well tolerated, and no intraoperative adverse events occurred.

Electroporation of tumor cells was performed using the Cliniporator VITAE device (IGEA S.p.A., Carpi, Italy), a medical-grade instrument designed for electrochemotherapy applications (Figure 2).

This system features six independently controlled and electrically isolated outputs, each capable of delivering eight rectangular pulses with a rise time of 1 μ s, a pulse duration of 100 μ s, a maximum current of 50 A, and a voltage output of up to 3000 V.¹³ These parameters are optimized to induce transient permeabilization of the tumor cell membranes, thereby enhancing intracellular uptake of chemotherapeutic agents. Prior to pulse delivery, bleomycin (Bleomycin Nippon Kayaku, Sanofi Aventis, Milan, Italy) was administered intralesionally at a concentration of 1,000 IU/mL. This localized administration ensured high drug concentration within the tumor microenvironment while minimizing systemic exposure and associated toxicity. Following local administration of bleomycin, electric pulses were delivered approximately 10 minutes later to maximize drug uptake by tumor cells. Postoperatively, management focused on careful pain control, prevention of secondary infection, glycemic monitoring due to diabetes, and surveillance of the expected necrotic phase following ECT. These precautions ensured safe treatment delivery in this frail patient population.

Results

Histology

The histological sample shows an epithelial proliferation of squamous type, consisting of nests and cords of atypical cells infiltrating the underlying dermis. The neoplastic cells exhibit marked nuclear pleomorphism, hyperchromatic nuclei, and

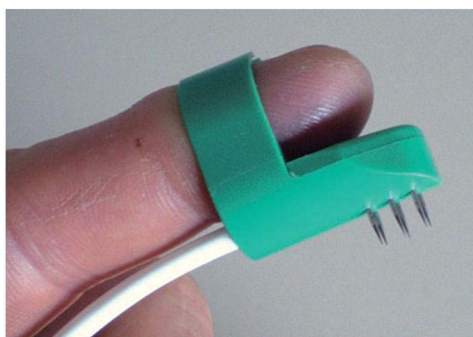


Figure 2 The needles used for the treatment of the lesion and the perilesional area.



Figure 3 Twenty days after the treatment, small areas of desquamation and necrosis are observed.

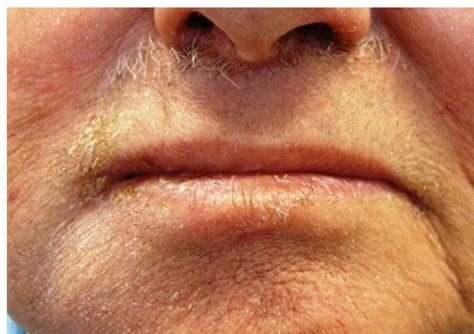


Figure 4 Three months after the treatment, complete healing of the lesion is observed without any scarring.

increased nuclear-to-cytoplasmic ratios. Numerous mitoses are evident, including atypical ones. Focal areas of keratinization are observed; however, there is an overall loss of squamous maturation and architectural disorganization, consistent with a moderate to poorly differentiated grade. The tumor border appears infiltrative, with a perilesional chronic inflammatory reaction. No glandular or specific mucinous component is present. The diagnosis is moderately to poorly differentiated squamous cell carcinoma of the labial commissure, infiltrating the dermis. Resection margins are not assessable in the current specimen.

Clinical Results

A single treatment session of ECT was sufficient to achieve the desired outcome. In the postoperative period, controlled necrosis of the lesion was observed, followed by progressive healing by secondary intention, with excellent aesthetic and functional results. Areas of necrosis persisted for approximately 30 to 60 days, and complete restitutio ad integrum was achieved after 3 months (Figures 3 and 4). The oral commissure remained intact, and there was no impairment of the orbicularis oris muscle function. After four years, no recurrence was observed, further follow-up was not possible, as the patient had died of a heart attack.

Discussion

The outcome of this case report demonstrates complete healing of the lip in a patient affected by squamous cell carcinoma, with a complex medical history including chronic kidney disease, diabetes, hypertension, and previous ischemic heart disease. Electrochemotherapy has been previously described for cutaneous squamous cell carcinoma; however, reports specifically addressing lower-lip SCC in elderly patients with significant comorbidities remain limited. This result was made possible thanks to the studies that, for the first time, demonstrated how electroporation can significantly enhance the cytotoxicity of drugs such as bleomycin, paving the way for electrochemotherapy as a therapeutic approach.¹⁴ The application of a high-voltage electric pulse following the administration of bleomycin

resulted in a significant reduction in the size of AH-109A hepatocellular carcinoma, which had been subcutaneously inoculated in Donryu rats. The treatment led to a 17% reduction in tumor mass within four days. Neither the high-voltage electric pulse nor the administration of bleomycin alone showed inhibitory effects on tumor growth, leading to the conclusion that the combined use of a high-voltage electric pulse and an antitumor drug has potential applications in cancer treatment.¹⁵ Moreover, the increasing incidence of cutaneous squamous cell carcinoma, particularly in sun-exposed areas such as the lip, highlights the clinical importance of developing effective and minimally invasive treatment options.¹⁶ Although surgical excision is the standard treatment with high cure rates, a significant subset of patients with advanced or recurrent lip squamous cell carcinoma are not suitable for surgery due to functional or cosmetic concerns. The study by Bertino et al evaluated 162 patients with cSCC, with a mean age of 80 years, across 18 European centers, reporting a complete response rate of 62% and a partial response rate of 21%, with only mild side effects.¹⁶ Elderly patients with metastatic disease showed a complete response rate of 57% and durable local control.¹⁷ However, none of these studies systematically characterize the burden of comorbidities, nor do they specifically isolate the outcomes of ECT for lower lip carcinoma in elderly populations with significant comorbidities. This confirms that targeted evidence in this specific subgroup remains limited. The literature highlights a knowledge gap regarding the optimal application of electrochemotherapy specifically for lip squamous cell carcinoma, including standardized protocols, long-term outcomes, and integration with emerging therapies such as immunotherapy.¹⁸

Numerous studies have reported response rates to ECT ranging from approximately 38% to 100%, with particularly favorable outcomes observed in small, primary, and treatment-naïve tumors.¹⁹ In fact, it is evident that primary tumors respond significantly better than recurrent or previously treated lesions. Moreover, combining ECT with immunotherapy appears to further enhance therapeutic efficacy, improving response rates compared to ECT alone.

The effectiveness of electrochemotherapy has shown high objective response rates, with complete response rates ranging from 50% to 100% in squamous cell carcinoma of the lip and head and neck regions, demonstrating ECT's efficacy in tumor control.²⁰ Despite encouraging results, response rates vary widely across studies, partly due to heterogeneous patient populations, tumor stages, and prior treatments.²¹ Many studies are retrospective or involve small cohorts, limiting statistical power and the robustness of conclusions.²²

The lack of randomized controlled trials specifically focused on lip SCC restricts definitive efficacy assessments. In fact the Electrochemotherapy is generally well tolerated, with mild and manageable side effects such as local pain, edema, and ulceration.²³

Several studies emphasize the preservation of organ function and aesthetic outcomes, which are crucial in squamous cell carcinoma of the lip due to its anatomical and functional significance.

Improvements in quality of life, including pain reduction and bleeding control, have been reported by several authors. Some reports have noted serious adverse events, such as bleeding and osteoradionecrosis, particularly in large or heavily pretreated tumors.²⁴

Variability in anesthesia protocols and electrode types may contribute to inconsistent safety profiles. Data on long-term functional outcomes and late toxicity remain limited, hindering a comprehensive safety assessment. The combination of electrochemotherapy with immunotherapy, particularly with PD-1 inhibitors, shows potential in enhancing objective response rates and improving symptom control, thereby contributing positively to patients' quality of life.¹⁸ The immunomodulatory effects of ECT, including the induction of systemic immune responses, provide a strong scientific rationale for integrating these two therapeutic strategies. However, the currently available evidence remains limited and further clinical studies are needed to confirm the efficacy and safety of this combined approach. The literature on ECT for SCC of the lip and related head and neck tumors highlights promising efficacy and safety profiles, particularly in patients who are not eligible for conventional treatments. Studies consistently report favorable objective response rates and improvements in quality of life, underscoring the potential of ECT as both a curative and palliative option. However, variability in study designs, small sample sizes, and heterogeneity in tumor sites and treatment protocols limit the generalizability of the findings. This case is important because evidence on the use of electrochemotherapy for lower lip SCC in elderly patients with multiple comorbidities is still limited. Our report contributes clinically relevant observations regarding safety, functional preservation, and long term tumor control in a fragile patient not eligible for surgery or radiotherapy. This case demonstrates that electrochemotherapy represents a safe, effective, and function-preserving option for the management of lower-lip squamous cell carcinoma in elderly patients with

significant comorbidities. The treatment achieved complete tumor regression, excellent aesthetic restoration, and long-term local control without morbidity. Given the limited surgical tolerance and increased risk associated with conventional treatments in frail patients, electrochemotherapy should be considered a valuable alternative in selected cases. Further studies focusing specifically on elderly and comorbid populations are needed to better define indications and long-term outcomes.

Conclusion

The outcome of this case report shows the high clinical efficacy of ECT in the treatment of SCC of the lip region. The observed outcomes support its therapeutic potential, both in terms of local disease control and quality-of-life improvement, making it a valuable option in selected cases. Although this is a single case report, our experience suggests that ECT may offer a valuable alternative for patients with SCC of the lip, particularly when conventional treatments are not feasible.

Data Sharing Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

Ethics Approval

The authors confirm that the approval of an institutional review board was not required for this work. This retrospective review of patient data did not require ethical approval in accordance with national guidelines.

Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images and videos.

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Disclosure

The authors have no conflicts of interest to declare in this work.

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