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Scientific contribution/Original research

# Electrochemotherapy with a Reduced Dose of Bleomycin in the Treatment of Advanced Skin Cancer. A Case Study

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## Abstract:

Squamous cutaneous skin cancer is common cancer with increasing incidence. Commonly is treated with surgery or radiotherapy, but a new technique has been emerging in recent years. Electrochemotherapy (ECT) is innovative and still developing treatment of malignant tumors, especially effective in treating cutaneous malignancy. Its feasibility and efficacy have been proven in elderly patients with comorbidities who cannot undergo standard treatments. Some recent studies have focused on reducing bleomycin dose in elderly patients to minimize side effects and concurrently obtain the same treatment outcome. This article presents a case study of an elder patient with advanced skin cancer, treated with electrochemotherapy with a reduced bleomycin dose, where a complete response was observed in a long-term follow-up period.

**Keywords:** Electrochemotherapy; Bleomycin; Reduced dose; Squamous cell carcinoma; Elderly patient

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## 1. Introduction

Besides basal cell carcinoma, cutaneous squamous cell carcinoma is the second most common non-melanoma skin cancer with increasing worldwide incidence rates (Muzic et al., 2017). The risk factors are UV exposure, skin type and immunosuppression (Schmitt et al., 2011). Most common cutaneous squamous cell carcinoma arise in the face region and are clinically presented as a form of a red scaly plaque with different degrees of infiltration (Waldman & Schmults, 2019).

Cutaneous squamous cell carcinoma rarely form metastases in the regional lymph nodes, but the metastases are associated with a poor prognosis. There is a higher risk for metastasis and local recurrence in tumors greater than 20mm and depth of invasion (DOI) more than 2 mm. Poor prognostic factors also include extensive perineural involvement and poor tumor differentiation (Burton et al., 2016).

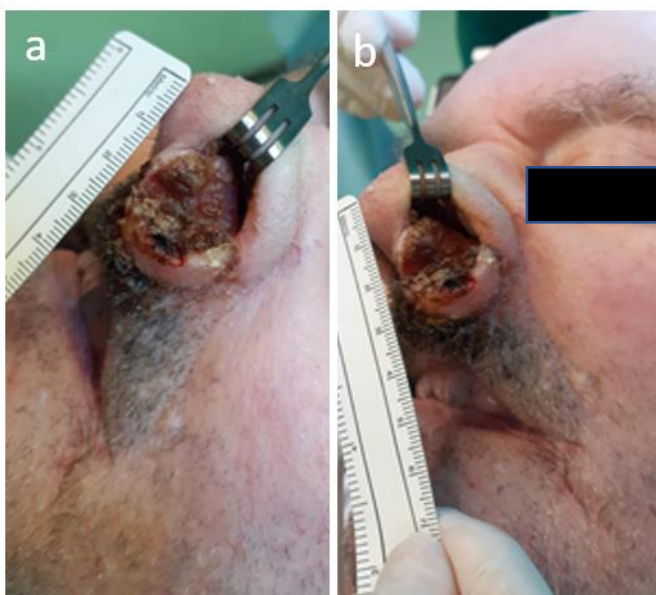
Standard treatment for most patients is complete excision of the carcinoma, especially when a tumor is small and in a favorable location. Radiotherapy is an alternative treatment in circumstances where surgery could result in significant esthetic or functional deficit (nose, eyelids, lips, ear), in elderly patients with comorbidities and in patients reluctant to surgery (Burton et al., 2016). In recent years ECT is emerging as a novel, local ablative treatment with comparable results to other modalities (Clover et al., 2020). In the presented case study, we address the role of ECT in the treatment of elderly patients with advanced skin cancers.

## 2. Patients and Methods

### 2.1. Patient characteristics

The ninety-year-old patient with advanced dementia and severe comorbidities (severe heart failure, diabetes and chronic renal failure) was admitted to the Department of Otorhinolaryngology and Cervicofacial Surgery, University Medical Centre Ljubljana due to protruding mass from his left nostril. Two years before, an excision of cutaneous squamous cell carcinoma from the scalp region was performed. An ENT clinical exam revealed a solitary suspicious mass of size around 30 mm, arising from the left side of the nasal columella (**Figure 1**). Biopsy was taken from the mass and histopathological findings confirmed squamous cell carcinoma metastasis.

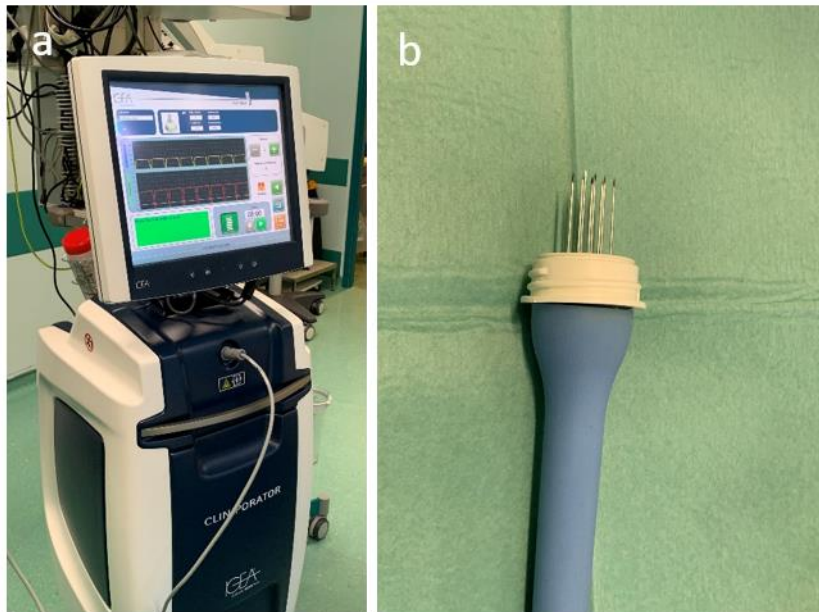
A detailed diagnostic workup, including CT scans, did not detect any other regional or distant metastases. The patient was presented on the multidisciplinary head and neck tumor board and the indication for ECT treatment was agreed upon by all members.



**Figure 1.** Two views on the patient with metastasis of squamous cell carcinoma to the nasal columella.

## 2.2. Electrochemotherapy procedure

The electrochemotherapy procedure was performed according to the recommendations of Update Standard Operating Procedure for electrochemotherapy under sedation anesthesia (Gehl et al., 2018). The reduced dose 18000 IU of bleomycin (BLM) (10 000 IU/m<sup>2</sup>, Heinrich Mack Nachf. GmbH & CO. KG, Illertissen, Germany) was intravenously administered in bolus. After 8 minutes, metastasis was treated with linear electrodes. 5 electric pulses, each in duration of 100  $\mu$ s, were delivered by electric pulse generator Cliniporator Vitae® (IGEA, Carpi, Italy) (**Figure 2**). The procedure was finished 13 minutes after BLM administration.



**Figure 2.** Electric pulse generator (a) and linear electrode (b) used in the treatment

## 3. Results

During the procedure and recovery time, we did not record any complications that would need additional medical interventions. Metamizole was used for the prevention of pain immediately after the treatment. The patient was discharged from the hospital the next day.

In the first follow-up visit two weeks after ECT, mild inflammation and ulceration were observed (grade I to II according to CTCAE ver. 4.0) (Chen et al., 2012). In the following weeks the wound healed spontaneously without any surgical intervention. After two months, the complete response was obtained and persisted more than one year after ECT (**Figure 3**).



**Figure 3.** Patient one year after treatment with electrochemotherapy.

#### 4. Discussion

ECT is a local ablative tumor treatment with proven antitumor efficacy in preclinical and clinical studies (Bertino et al., 2016; Sersa et al., 1997). It has already been spread across more than 170 centers in Europe (Clover et al., 2020). In ECT, the electric field is used to increase membrane permeability and thus enhance the uptake of cytotoxic drugs into the tumor cells. Besides the direct antitumor effect, ECT also impacts tumor vascularization and provokes a local immune response, which both potentiate the effectiveness of treatment (Yarmush et al., 2014). Currently, two cytostatics are used in ECT – BLM and cisplatin (Gehl et al., 2018). Preclinical studies demonstrated that electroporation increases the effectiveness of BLM several 1000 times and of cisplatin up to 70 times (Miklavčič et al., 2014; Sersa et al., 2008).

The patient in our study had an advanced stage of cancer disease and several comorbidities. Consequently, surgery in general anesthesia could significantly hamper a patient's underlying diseases. Excision in local anesthesia was not possible due to the size and location of the tumor. Radiotherapy as an alternative treatment was not suitable because of the patient's lack of ability to keep still for the required time during irradiation. ECT was chosen as the only curative treatment option for the particular patient. According to our case study, we believe that ECT is not suitable only as a primary treatment for skin tumors (Clover et al., 2020), but it exceeds in use to other cases in which the standard modalities cannot be used due to different causes.

Another important conclusion of our study is that ECT can be safely performed in sedation. Since the whole procedure is done in a few minutes, the sedation is light and short; thus, the recovery time is faster. Our patient did not have any side effects during and after sedation, and he was discharged the following day.

ECT has a response rate between 60-80 %, comparable to other skin ablative techniques (Clover et al., 2020). Tumors with the highest responses are basal cell carcinoma. In addition to histological types, tumors differ in responses regarding tumor size (larger tumors are less responsive), and previous treatments, which decrease the rate of complete responses (Bertino et al., 2016; Clover et al., 2020; Marty et al., 2006). Despite the advanced stage of the cancer disease, a reduced dose (10.000 IU/m<sup>2</sup>) of BLM was used in our study. The decision to use the reduced BLM dose was based on the study of the pharmacokinetics of bleomycin in elderly cancer patients. This study demonstrated that a decline in lean body mass, total water content, and impaired renal function lead to decreased BLM elimination. Consequently, a prolonged higher serum concentration of BLM might be obtained when using a standard (15.000 IU/m<sup>2</sup>) BLM dose (Groselj et al., 2016). To the best of our knowledge, only a few clinical studies till now have shown that ECT with a reduced dose of BLM is equally efficient as ECT with a standard dose (Groselj et al., 2016; Jamsek et al., 2020; Rotunno et al., 2018).

In our case, two months after ECT, the complete response was recorded and persisted in the last follow-up visit more than a year after the treatment. Recently, Jamsek et al. (2020) published long-term results comparing reduced and standard BLM doses in ECT treatment, and they did not observe any statistically significant difference in long-term tumor control between both groups. It should be noted that tumors in their study were primary skin cancers; most of them were basal cell carcinomas with a median tumor diameter of 21mm. Our patients had unfavorable prognostic factors (regional metastasis and size more than 30 mm) that might worsen the probability of a complete response.

It is also important to emphasize that the healing process was favorable, with minor side effects that did not need additional wound dressing. The wound was healed in less than two months without any functional deficits and an excellent final cosmetic outcome. This is in concordance with the results of Groselj et al, who recorded a shorter healing time and better cosmetic results with a reduced dose of BLM in elderly patients (Strojan & Groselj et al., 2021).

#### 5. Conclusions

ECT proved an efficient skin cancer treatment modality and was safely performed in sedation in old and comorbid patient. Specifically, in the elderly patient a reduced dose of BLM was efficient. More data is needed on optimal BLM dose. Our results warrant further investigations in the form of properly designed and well-conducted prospective clinical trials.



**Institutional Review Board Statement:** The study was conducted according to the guidelines of the Declaration of Helsinki.

**Conflicts of Interest:** The authors declare no conflict of interest.

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