International Journal of Dermatology

Original Article

The role of electrochemotherapy in the treatment of locally advanced or recurrent eyelid-periocular basal cell carcinoma: long-term results

Attila Vass,[1] Nóra Polgár,[1] Szilvia Alexa Sándor,[1] Dóra Ágoston,[2] Petra Rózsa,[2] Ildikó Csányi,[2] Henriette Ócsai,[2] Eszter Baltás,[2] Judit Oláh,[2,3] Erika Gabriella Kis,[2] and Edit Tóth-Molnár,[1,4]

[1]Department of Ophthalmology, University of Szeged, Szeged, Hungary, [2]Department of Dermatology and Allergology, University of Szeged, Szeged, Hungary, [3]Department of Oncotherapy, University of Szeged, Szeged, Hungary; and [4]Faculty of Health Sciences and Social Studies, University of Szeged, Szeged, Hungary

Keywords
electrochemotherapy; eyelid; basal cell carcinoma; periocular region; skin cancer; BCC; ECT.

Correspondence
Edit Tóth-Molnár
Department of Ophthalmology
University of Szeged
10-11 Korányi Fasor
Szeged 6720
Hungary
E-mail: tme@tmedit.hu

Conflict of interest: None.

Funding source: None.

doi: 10.1111/ijd.17346

Abstract

Background While electrochemotherapy (ECT) is increasingly utilized as a highly effective method in the treatment of tumors in the head and neck region, there is significantly less data available for eyelid-periocular skin tumors. Our group reported the first extensive case series of eyelid-periocular basal cell carcinoma (BCC) patients with short-term follow-up treatment with ECT. The present study aims to report our long-term results of eyelid-periocular BCC cases treated with ECT.

Methods The treatments were performed according to the ESOPE (European Standard Operating Procedures on Electrochemotherapy) guidelines using the Cliniporator™ device. All patients received bleomycin-based ECT, administered intratumorally or intravenously. Tumor response was evaluated using the RECIST 1.1 criteria.

Results The results of 19 patients treated with ECT are presented. Four patients had locally advanced primary tumors, while 15 patients had recurrent tumors. Bleomycin was administered intratumorally in four patients and intravenously in 15 patients. The overall response was 100%, while the complete response rate proved to be 95%. In three cases (15.8%), recurrence was observed during the mean follow-up period of 78.9 months.

Conclusions ECT can effectively treat locally advanced or recurrent BCC in the eyelid-periocular skin region. Excellent tumor control can be achieved with good functional and cosmetic results without systemic adverse events with long interval follow-up.

Introduction

Basal cell carcinoma (BCC) is the most common human malignancy. The incidence of affected individuals has continuously increased for many years, with epidemiological data indicating an annual incidence growth rate of 1–3%. Chronic sun exposure, in addition to skin phototype, stands out as the primary risk factor for the development of BCC. Since the head and neck, especially the periocular skin region, receive the most intense sun exposure, BCC predominantly manifests in these areas.[1,2]

The gold standard for the treatment of BCC in the head and neck area is surgical removal of the tumor in a proper manner, preferably with intraoperative histological control of the excision margins if possible (Mohs surgery). In cases of inoperable tumors (e.g., where bone involvement occurred), incompletely removed malignancies, or as adjuvant therapy in the presence of perineural invasion, irradiation can be highly effective. Patients with locally advanced, recurrent, or metastatic BCCs can benefit from systemic treatment with hedgehog or programmed death-1 inhibitors.[3–5] Despite all these therapeutic options, treating locally advanced/recurrent BCCs remains challenging. However, these difficulties are particularly pronounced in the periocular-eyelid area. While primarily considering oncological aspects and patient safety in determining the therapeutic plan, other factors should also be considered when treating

advanced BCC in the periocular region.[6] For elderly patients with comorbidities, the surgical removal of large tumors and the reconstruction of tissue defects often pose a substantial surgical burden. In surgeries of the periocular skin area, it is crucial to consider that more extensive excisions requiring significant reconstruction may alter the patient's self-image, potentially leading to the development of severe psychological disorders. Beyond oncological, patient safety, and cosmetic factors, preserving and restoring eyelid function are also of fundamental importance after extended surgery. The homeostasis of the ocular surface relies on the eyelid's proper functioning. If there is significant disruption in the kinetics of eyelid closure and opening, the integrity of the ocular surface may be compromised. In severe cases, the cornea may lose its transparency, threatening vision loss.[7]

A novel option for the treatment of primary malignant and metastatic solid tumors of many histotypes located on the skin is electrochemotherapy (ECT), which has gradually become a widely used therapeutic procedure over the past 20 years. In addition to cutaneous malignancies, this procedure is now successfully applied to treat deep-seated tumors and visceral cancers as well.[8–12] The basic principle of ECT is electroporation, when short-duration, high-voltage electric pulses temporarily create pores in the cell membrane. The transient permeation of the cell membrane allows the entry of large, non-soluble, or poorly permeant, water-soluble chemotherapeutic agents into the cytosol.[13] After the cessation of the electric pulses, the pores close, restoring the integrity of the cell membrane. Consequently, any cytotoxic substances that enter the cytosol become trapped inside the cell. In this manner, the cytotoxic agent that has entered the cell can exert its cytolytic effect, amplifying the cell-killing capacity. Bleomycin and cisplatin have proven to be the most effective chemotherapeutic agents in ECT, leading to the widespread use of these two drugs in clinical practice.[14,15] During ECT, the cytotoxicity of bleomycin increases several hundredfold, while that of cisplatin rises to a lesser but still significant extent.[16]

While ECT is increasingly utilized as a highly effective method in the treatment of tumors in the head and neck region, there is significantly less data available on eyelid-periocular skin tumors.[17–20] The first extensive case series of eyelid-periocular BCC patients treated with ECT was reported by our group in 2019.[21] The follow-up period in that study (median: 19 months) was not long enough to assess the recurrence-related efficacy. Therefore, only moderate consequences could be deduced. In the present retrospective observational study, we report the long-term results of our locally advanced/recurrent eyelid-periocular BCC cases treated with ECT.

Patients and Methods

Patients

To assess the long-term efficacy of ECT treatment, the present study included all patients with locally advanced or recurrent eyelid-periocular BCC who underwent an ECT procedure at the Department of Dermatology and Allergology at the University of Szeged between May 2014 and October 2018 and had a minimum of 5 years (60 months) or longer follow-up period.

The study was approved by the Institutional Review Board of the University of Szeged (ECT-REPRO-002, 9/2016-SZTE) and conducted in accordance with the principles of the Declaration of Helsinki. All patients gave their written informed consent prior to treatments. Additionally, informed consent was obtained from all patients for the publication of identifying information/images in an online open-access publication.

Methods

All patients underwent detailed dermatological and ophthalmological examinations. In cases where clinical examination suggested the presence of bone involvement, orbital computed tomography was performed. In the case of bone involvement, the patient was not suitable for ECT treatment.

The clinical characteristics of the tumors, such as the size, number, localization, and type (primary or recurrent) of the lesions, were meticulously recorded before the ECT procedure. Biopsy of the tumor tissue was performed in all cases prior to ECT treatment. Treatments were performed according to the ESOPE guidelines using the Cliniporator™ (IGEA Ltd, Modena, Italy) device.[16] Every patient received bleomycin-based ECT; the route of administration was intratumoral or intravenous. The technical parameters of the treatment protocol were described earlier by our group.[21] In brief, electric pulses were applied by standard needle electrodes after 1 or 8 min following intratumoral or systemic bleomycin administration, respectively. Needle electrodes with linear (N-20-4B) or hexagonal (N20-HG and N-30-HG) configurations or plate electrodes (P-30-8B) were used.

The electrical parameters of treatments with row needle electrodes were 8 square wave pulses 1000 V/cm for 100 ms at 5 kHz, with hexagonal electrodes, 4 square wave pulses 910 V/cm for 100 ms at 5 kHz. Depending on the clinical tumor status (number, location, and size of the lesions), general anesthesia with endotracheal intubation or laryngeal mask was used. Following the treatment, all patients were observed in the hospital for 1 day to closely monitor potential adverse events such as nausea and flu-like symptoms. Simple non-adhesive dressings were applied to the wounds, and antibiotic eye drops (ofloxacine) were prescribed for 6–10 days.

Tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.[22] Complete response (CR) was diagnosed in case of the disappearance of the target lesion, while partial response (PR) was defined when at least a 30% decrease in the baseline sum of the longest diameter of the target lesion was observed. The treatment strategy for each patient was personalized, determined primarily by the tumor response to the initial treatment.

According to our protocol, the criteria for ECT re-treatment were based on the observation of PR 6 weeks after the initial ECT treatment, with a two-month time interval between the first and second ECT sessions.

Patients were closely monitored after the treatments: They were examined and photo-documented twice in the first month, monthly in the following five months, bimonthly in the first year, quarterly in the second year, and every six months after that.

Only BCCs in the eyelid-periocular localizations were included in the statistical analysis.

Statistical analysis

SPSS software version 17.0 (SPSS, Chicago, IL, USA) was used for statistical analysis.

Results

Between May 2014 and October 2018, 19 patients with eyelid-periocular BCCs were treated with ECT and had a clinical follow-up of at least 60 months. All patients included in the study were of Caucasian descent (12 male and 7 female, mean patient age: 75.9 years, median: 72 years, range: 11–86 years). The follow-up interval was between 61 and 112 months (mean: 78.9 months, median: 72 months). Detailed characteristics of the treated cases can be found in Table 1.

Bleomycin was administered intratumorally in four patients and intravenously in 15 patients. For intratumoral administration of bleomycin, 1000 IU/ml concentration was used. The volume was calculated based on the size of the lesion (250-1000 IU/cm^3), while the systemic dose was 15,000 IU/m^2. The tumor volume was calculated as follows: $ab2\pi/6$, where a = longest diameter, b = longest diameter perpendicular to a. After tumor volume calculations, the given volume and concentrations of bleomycin were defined according to the updated ESOPE protocol. After performing intratumoral bleomycin injection, blanching of the lesion and the surrounding tissue up to the planned safety margin was carefully checked to ensure the entire tumor volume was covered. Safety margins were determined according to surgical margins recommended in the guidelines.

Intravenous administration was indicated in patients with multiple tumors, including those with extraperiocular skin localization.

The summary of the results of the treated cases can be found in Table 2.

Six months after the treatment, CR was achieved in 18 patients (95%); we observed PR in one patient. Among 19 patients who met the criteria for long-term follow-up, recurrence was observed in 3 cases (15.8%). In one case, a child with xeroderma pigmentosum, the continuous appearance of BCCs and squamous cell carcinomas throughout the body was noted. When the xeroderma pigmentosum case was excluded from the statistical analysis, a 5-year recurrence-free tumor control rate was achieved in 17 patients (89.5%). The rationale for the exclusion is that xeroderma pigmentosum is a genetically determined disorder in which the applied surgical treatment barely influences the development and continuous appearance of malignant skin tumors. Therefore, the recurrence does not reflect the effectiveness of the therapy.

For the other two patients who experienced recurrence (10.5% of all patients), tumor relapse occurred 24 and 27 months after ECT treatment. After re-treatment with ECT, complete remission was achieved in both patients, and this state signifies lasting recurrence-free status for both of them, as they have been in a tumor-free condition for 42 and 67 months, respectively.

In two other patients, recurrence was observed only in tumors located in the extraperiocular region and not in those located in the periocular region.

The highest number of treatment sessions was linked to genetic susceptibility for developing various types of skin malignancies: our patient with xeroderma pigmentosum has undergone six applications in the periocular skin area thus far. In the case of 3 patients with lower eyelid BCC, the contracting post-ECT scar caused ectropion, which was surgically corrected 6–8 months after the ECT. No systemic side effects from bleomycin were observed in any of the cases. Furthermore, up to the first 2 months following the treatment, skin ulceration accompanied by mild edema developed on the treated skin surface. However, it was ultimately resolved in all cases. Figure 1 demonstrates a lower eyelid BCC patient before (A) the ECT treatment, 3 months (B), and 3 years after the procedure (C).

Discussion

Approximately 75% of BCCs develop in the head and neck region, with around 20% involving the periocular area.[23] Close to two-thirds of malignant tumors in the head and neck region are diagnosed in locally advanced stages. Despite aggressive and often multimodal treatment protocols, there is a high risk of local recurrence.[24–26]

The treatment of locally advanced or recurrent periocular BCCs is a complex task. In spite of the expanding therapeutic options, the treatment of large or recurrent periocular skin malignancies remains a significant challenge, highlighting the importance of the emergence and integration of new therapeutic modalities into clinical practice.[6,27,28] In the modern oncotherapeutic toolkit, the role and significance of ECT are becoming increasingly well-defined. The range of tumor types effectively treated with good results is exponentially expanding thanks to rapid developments.

In the field of ophthalmology, ECT has recently gained attention as a potential therapeutic option. Our group has routinely applied the procedure in patients with challenging periocular BCC since 2014. In our previous examination, none of the 12 patients treated with 12 ECT sessions experienced tumor recurrence during the median 19-month follow-up period.[21] Summarizing our long-term results, it can be concluded that the

Table 1 Detailed characteristics of the eyelid-periocular skin basal cell carcinoma cases treated with ECT

	Age (year)/ gender	Periorbital localization	Other localization	Size of periocular tumor/s (mm)	Primary/rec./ (previous treatments)	Route of BL	Type of electrode / average current(A)	Follow-up (month)	Number of ECT treatment (dates of treatment)	Results	Rec.: localization and time interval after the first session(s) of ECT
1	83/F	Lower eyelid, eyebrow	Both hands, nose	10 × 13	Recurrent (surgery)	iv	N-20-HG, P-30-8B	98	1	CR	No rec.
2	72/M	Lower eyelid	Fronto-temporal region, cheek	43 × 27	Recurrent/multiple surgeries) vismodegib	IV	N-20-4B, N-20-HG	94	3 (2 + 1) (2 months interval)	CR	Rec.: 27 months after first sessions of ECT lower eyelid, fronto-temporal area (treatment of recurrence: ECT)
3	44/F	Eyebrow, upper eyelid	—	10 × 25	Recurrent/surgery		N-20-HG	112	2 (2 months interval)	CR	No rec.
4	81/M	Medial canthal region	Head, face area	7 × 9	Recurrent/surgery	IT	N-20-HG	74	1	CR	No rec.
5	77/F	Lower eyelid	Both hands, nose	13 × 10	Recurrent after surgery	iv	N-20-HG	70	1	CR	No rec.
6	35/F	Eyebrow, upper eyelid	—	25 × 10	Recurrent/surgery	it	N-20-HG	97	2 (2 months interval)	CR	No rec.
7	11/F	Upper eyelid, lower eyelid, both canthal regions	Nose, perioral skin, frontotemporal area, entire skin surface xeroderma pigmentosum	6 × 8 12 × 5 20 × 15	Recurrent/surgery/ pembrolizumab	iv	P-30-8B, N-20-4B	110	6 in the periocular region	PR	Continous rec.
8	45/M	Upper eyelid	—	35 × 12	Recurrent/surgery	it	N-20-4B, P-30-8B	84	1	CR	No rec.
9	81/M	Both lower eyelids, medial canthi	Head-neck, back	15 × 110 8 × 15	Recurrent/surgery	iv	N-20-4B, N-20-HG	87	1	CR	No rec.
10	82/M	Lower eyelid, medial canthus	Nose	13 × 27	Recurrent/surgery	iv	N-30-HG, N-20-4B	74	2 (2 months interval)	CR	No rec.
11	80/F	Lower eyelid, medial canthus	Head, neck, trunk	10 × 15 5 × 8	Recurrent/surgery	iv	N-20-4B, P-30-8B	69	2 (2 months interval)	CR	No rec.
12	66/M	Lateral canthus, upper eyelid	Head-neck, trunk, arm, labial area Gorlin-Goltz syndrome	8 × 6 5 × 4	Recurrent/surgery	iv	N-20-HG	71	2 in the periocular region with 2 months interval 2 in other localization (trunk, arm, labial area)	CR	No rec.
13	72/M	Lower eyelid, medial canthal region	Head-neck, chest, upper extremities	7 × 5 2 × 3	Recurrent/surgery PDT, pembrolizumab	iv	N-20-4B	72	1 in the periocular region, 2 in other localization	CR	No rec. in the periocular skin area Chest: rec. (treatment: one ECT session)
14	86/M	Lateral canthal region	Trunk, head-neck, extremities	25 × 25	Periocular: primary trunk: surgery	iv	N-20-4B	70	1 in the periocular area 1 retreatment in other localization	CR	No rec. in the periocular skin area Head: rec. (treatment: one ECT session)

Table 1 Continued

	Age (year)/ gender	Periorbital localization	Other localization	Size of periocular tumor/s (mm)	Primary/rec./ (previous treatments)	Route of BL	Type of electrode / average current(A)	Follow-up (month)	Number of ECT treatment (dates of treatment)	Results	Rec.: localization and time interval after the first session(s) of ECT
15	64/M	Lower eyelid, medial canthus	Trunk, head-neck, extremities	14 × 14	Primary	iv	N-20-4B	68	2 (2 months interval)	CR	No rec.
16	31/M	Lower eyelid, medial canthal area, nose	—	40 × 40	Primary	iv	N-20-4B	66	3 (2 + 1) (2 months interval)	CR	Rec.: 24 months after first sessions of ECT (treatment: ECT)
17	70/M	Lower eyelid	Scalp, neck	20 × 15	Primary	iv	N-20-4B	62	1	CR	No rec.
18	72/F	Lateral canthus	Trunk, head, multiplex	15 × 12	Recurrent/surgery	iv	N-20-4B	61	1	CR	No rec.
19	74/M	Lower eyelid, medial canthus	Head, neck, multiplex	14 × 20 4 × 4	Recurrent/surgery	iv	N-20-4B, N-20-HG	61	2 (2 months interval)	CR	No rec.

BI, bleomycin; CR, complete response; it, intratumoral; iv, intravenous; N-20-4B, needle electrodes with linear configuration; N20-HG, N-30-HG, needle electrodes with hexagonal configurations; P-30-8B, plate electrodes; PR, partial response; rec, recurrence.

Table 2 Summarized characteristics of the treated cases

Characteristics of the treated cases	No of patients (%)
Primary BCC	4 (21)
Recurrent BCC	15 (79)
Localization	
Only on the periocular skin	4 (21%)
Multiple localizations	15 (79%)
Sessions of ECT in periocular localization: number of treated patients	1: 9 (47%) 2: 7 (37%) 3: 2 (10.5%) 6: 1 (5%)
Route of bleomycin administration:	
Intratumoral	4 (21%)
Intravenous	15 (79%)
Response	
Objective response	19 (100%)
Complete remission	18 (95.0%)
Partial remission	1 (5.0%)
Recurrences	3 (15.8%)
Excluding xeroderma pigmentosum case	2 (10.5%)
Follow-up time: mean 78.9 months overall tumor control (no recurrences)	84.2%
Excluding xeroderma pigmentosum case	89.5%

achieved overall response of 100% and the CR rate of 95% represent an excellent tumor response and reasonable long-term tumor control. During the mean follow-up period of 78.9 months, 10.5% of the patients experienced local recurrence. Considering that the treated tumors were high-risk BCCs, known to pose a higher risk of recurrence, these results are even more remarkable. Comparing our results with large cohorts of ECT treatments can be beneficial. The InspECT registry is the largest cohort of BCC patients with tumors of various locations treated with ECT.[29] The reported results, based on the statistical analysis of 623 BCC lesions from 330 patients in this registry, revealed an overall response of 96% and a CR of 85%. At a 17-month follow-up, 28 (9.3%) patients experienced local recurrence/progression.

While rigorous comparisons with other treatment options are challenging due to the general heterogeneity of published results, considering surgery as the gold standard of BCC treatment, some comparisons can help advance clinical practice. The 5-year recurrence rate after excision of primary BCC was reported to be 1–8%, while it ranged from 11.6% to 17.4% for recurrent lesions.[30,31] Comparing all these results, it can be concluded that for eyelid-periocular BCCs, ECT can be considered a curative-intent procedure even in cases of locally advanced and/or recurrent tumors.

In light of all these positive, encouraging results, the range of patients with periocular BCC treated with ECT has expanded in our recent clinical practice.

Previously, we primarily employed the procedure in cases of locally advanced primary tumors and recurrent lesions after

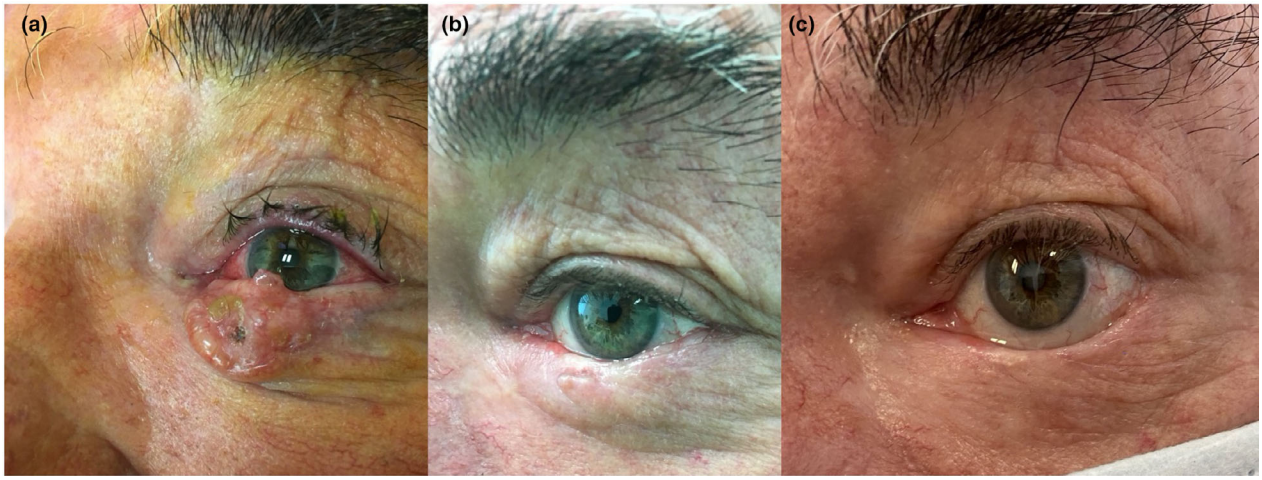

Figure 1 Electrochemotherapy (ECT) in the treatment of primary lower eyelid basal cell carcinoma. (a) Clinical appearance before the treatment. (b) Complete response 3 months after one session of ECT. (c) Tumor-free status and preserved function of the lower eyelid 3 years after the treatment

surgical excision and/or irradiation. At present, we often apply ECT treatment even in cases of primary tumors where surgical reconstruction might not necessarily result in optimal functional or cosmetic outcomes. For patients with widespread, multiple tumors throughout the body, ECT can be considered a frontline procedure.

The 2023-updated Consensus-Based Interdisciplinary Guideline for the Diagnosis and Treatment of BCC states that ECT can be utilized in treating locally advanced or recurrent BCC when standard treatments are not feasible.[32] Based on our experience in the periocular area, this therapeutic option can be utilized as a palliative measure and with curative intent. ECT can be an excellent option in cases where surgical excision would entail a significant surgical burden or when there is a higher risk of potentially impaired wound healing after surgical excision. The previously detailed thoughts are opinions based on the experiences of our center and are not therapeutic recommendations. Further studies are needed to support these notions.

While the number of our patients is sufficient to draw significant conclusions, considering all these aspects, we believe that ECT plays a substantial role in personalized treatment plans for eyelid-periocular BCC patients. It attains high oncological effectiveness while ensuring excellent function preservation and cosmetic results. ECT should always be considered a viable treatment alternative in cases requiring extended surgery.

Conclusion

ECT is an efficient and safe procedure compared to other methods, with noteworthy advantages being its repeatability and the high intratumoral chemotherapeutic concentration achieved with low systemic load. High rates of complete remissions and good long-term tumor-free outcomes can be achieved in the treated patients, demonstrating the efficacy of the procedure. Further increases in efficacy can be expected based on the continuously growing experience, optimizing intervention conditions, and delineating the patient subpopulation to be most effectively treated.[33–35]

Patient consent

All patients gave their written informed consent prior to treatment. Additionally, informed consent was obtained from all patients for the publication of identifying information/images in this online open-access publication.

Data availability statement

All data generated and analyzed during this study are included in the article as information files.

References

1 Ciążyńska M, Narbutt J, Woźniacka A, Lesiak A. Trends in basal cell carcinoma incidence rates: a 16-year retrospective study of a population in central Poland. *Postepy Dermatol Alergol*. 2018;**35**(1):47–52. https://doi.org/10.5114/ada.2018.73164
2 Dacosta Byfield S, Chen D, Yim YM, Reyes C. Age distribution of patients with advanced non-melanoma skin cancer in the United States. *Arch Dermatol Res*. 2013;**305**:845–50. https://doi.org/10.1007/s00403-013-1357-2
3 Migden MR, Chang ALS, Dirix L, Stratigos AJ, Lear JT. Emerging trends in the treatment of advanced basal cell carcinoma. *Cancer Treat Rev*. 2018;**64**:1–10. https://doi.org/10.1016/j.ctrv.2017.12.009
4 Lawrence CM. Mohs' micrographic surgery for basal cell carcinoma: Mohs' surgery for BCC. *Clin Exp Dermatol*. 1999;**24**:130–3. https://doi.org/10.1046/j.1365-2230.1999.00433.x

5 Stratigos AJ, Sekulic A, Peris K, Bechter O, Prey S, Kaatz M, et al. Cemiplimab in locally advanced basal cell carcinoma after hedgehog inhibitor therapy: an open-label, multicentre, single-arm, phase 2 trial. *Lancet Oncol*. 2021;**22**:848–57. https://doi.org/10.1016/S1470-2045(21)00126-1

6 Puig S, Berrucal A. Management of high-risk and advanced basal cell carcinoma. *Clin Transl Oncol*. 2015;**17**:497–503. https://doi.org/10.1007/s12094-014-1272-9

7 Martin I, Schaarschmidt ML, Glocker A, Herr R, Schmieder A, Goerdt S, et al. Patients preferences for the treatment of basal cell carcinoma: importance of cure and cosmetic outcome. *Acta Dermatol Venereol*. 2016;**96**:355–60. https://doi.org/10.2340/00015555.2273

8 Sersa G, Stabuc B, Cemazar M, Miklavcic D, Rudolf Z. Electrochemotherapy with cysplatin: the systemic antitumour effectiveness of cysplatin can be potentiated locally by the application of electric pulses in the treatment of malignant melanoma skin metastases. *Melanoma Res*. 2000;**10**(4):381–5. https://doi.org/10.1097/00008390-200008000-00010

9 Miklavcic D, Mali B, Kos B, Heller R, Sersa G. Electrochemotherapy: from the drawing board into the medical practice. *Biomed Eng Online*. 2014;**13**:29. https://doi.org/10.1186/1475-925X-13-29

10 Kis E, Baltás E, Kinyó E, Varga E, Nagy N, Gyulai R, et al. Successful treatment of multiple basaliomas with bleomycin-based electrochemotherapy: a case series of three patients with Gorlin-Goltz syndrome. *Acta Derm Venereol*. 2012;**92**:648–51. https://doi.org/10.2340/00015555-1361

11 Kis E, Oláh J, Ócsai L, Baltás E, Kemény L, Horváth AR. Electrochemotherapy of cutaneous metastases of melanoma—a case series study and systematic review of the evidence. *Dermatologic Surg*. 2011;**27**:816–24. https://doi.org/10.1111/j.1524-4725.2011.01951..x

12 Landström FJ, Nilsson COS, Crafoord S, Reizenstein JA, Adamsson G-BM, Löfgren AM. Electroporation therapy of skin cancer in the head and neck area. *Dermatologic Surg*. 2010;**36**:1245–50. https://doi.org/10.1111/j.1524-4725.2010.01617.x

13 Yarmush ML, Golberg A, Sersa G, Kotnik T, Miklavcic D. Electroporation-based therapy for medicine: principles, applications, and challenges. *Annu Rev Biomed Eng*. 2014;**16**:295–320. https://doi.org/10.1146/annurev-bioeng-071813-104622

14 Mir LM, Orlowski S, Belehradek J Jr, Paoletti C. Electrochemotherapy potentiation of antitumour effect of bleomycin by local electric pulses. *Eur J Cancer*. 1991;**27**:68–72. https://doi.org/10.1016/0277-5379(91)90064-k

15 Sersa G, Cemazar M, Miklavcic D. Antitumor effectiveness of electrochemotherapy with cis- diamminedichloroplatinum(II) in mice. *Cancer Res*. 1995;**55**:3450–5.

16 Mir LM, Gehl J, Sersa G, Collins CG, Garbay J-R, Billard V, et al. Standard operating procedures of the electrochemotherapy: Instructions for the use of bleomycin or cysplatin administered either systemically or locally and electric pulses delivered by the Cliniporator (TM) by means of invasive or non-invasive electrodes. *Eur J Cancer Suppl*. 2006;**4**:14–25. https://doi.org/10.1016/j.ejcsup.2006.08.003

17 Campana LG, Mali G, Sersa G, Valpione CA, Giorgi P, Strojan D, et al. Electrochemotherapy in non-melanoma head and neck cancers. Retrospective analysis of the treated cases. *Br J Oral Maxillofac Surg*. 2014;**52**:957–64. https://doi.org/10.1016/j.bjoms.2014.08.004

18 Campana LG, Testori A, Curatolo P, Quaglino P, Mocellin S, Framarini M, et al. Treatment efficacy with electrochemotherapy: a multi-institutional prospective observational study on 376 patients with superficial tumors. *Eur J Surg Oncol*. 2016;**42**:1914–23. https://doi.org/10.1016/j.ejso.2016.06.399

19 Salwa SP, Bourke MG, Forde PF, O'Shaughnessy M, O'Sullivan ST, Kelly EJ, et al. Electrochemotherapy for the treatment of ocular basal cell carcinoma; a novel adjunct in the disease management. *J Plast Reconstr Aesthet Surg*. 2013;**67**:403–6. https://doi.org/10.1016/j.bjps.2013.07.019

20 Schmelter M, Scheffka D, Kaune KM, Zutt M. Electrochmotherapy as a curative therapeutic approach for basal cell carcinoma of the eyelids. *J Dtsch Dermatol Ges*. 2022;**20**(5):690–3. https://doi.org/10.1111/ddg.14747

21 Kis EG, Baltás E, Ócsai H, Vass A, Németh IB, Varga E, et al. Electrochemotherapy in the treatment of locally advanced or recurrent eyelid, periocular basal cell carcinomas. *Sci Rep*. 2019;**9**:4285. https://doi.org/10.1038/s41598-019-41026-2

22 Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;**45**:228–47. https://doi.org/10.1016/j.ejca.2008.10.026

23 Saleh GM, Desai P, Collin JR, Ives A, Jones T, Hussain B. Incidence of eyelid basal cell carcinoma in England: 2000–2010. *Br J Ophthalmol*. 2017;**101**(2):209–12. https://doi.org/10.1136/bjophthalmol-2015-308261

24 Marur S, Forastiere AA. Head and neck cancer: changing epidemiology, diagnosis, and treatment. *Mayo Clin Proc*. 2008;**83**:489–501. https://doi.org/10.4065/83.4.489

25 Steiwert TY, Cohen WEE. State-of-the-art management of locally advanced head and neck cancer. *Br J Cancer*. 2005;**92**:1341–8. https://doi.org/10.1038/sj.bjc.6602510

26 Wang H, Zheng Z, Zhang Y, Bian C, Bao J, Xin Y, et al. Locally advanced head and neck squamous cell carcinoma treatment efficacy and safety: a systematic review and network meta-analysis. *Front Pharmacol*. 2023;**14**:1269863. https://doi.org/10.3389/fphar.2023.1269863

27 Shi Y, Jia R, Fan X. Ocular basal cell carcinoma: a brief literature review of clinical diagnosis and treatment. *Onco Targets Ther*. 2017;**10**:2483–9. https://doi.org/10.2147/OTT.S130371

28 Silverman N, Shinder R. What's new in eyelid tumors? *Asia-Pac J Ophthalmol*. 2017;**6**:143–52. https://doi.org/10.22608/APO.201701

29 Bertino G, Muir T, Odili J, Groselj A, Marconato R, Curatolo P, et al. Treatment of basal cell carcinoma with electrochemotherapy: insights from the InspECT Registry (2008-2019). *Curr Oncol*. 2022;**29**:5324–37. https://doi.org/10.3390/curroncol29080423

30 Mosterd K, Krekels GA, Nieman FH, Ostertag JU, Essers BA, Dirksen CD, et al. Surgical excision versus Mohs' micrographic surgery for primary and recurrent basal-cell carcinoma of the face: a prospective randomised controlled trial with 5-years' follow-up. *Lancet Oncol*. 2008;**9**:1149–56. https://doi.org/10.1016/S1470-2045(08)70260–2

31 Silverman MK, Kopf A, Bart RS, Grin CM, Levenstein MS. Recurrence rates of treated basal cell carcinomas. Part 3: surgical excision. *J Dermatol Surg Oncol*. 1992;**18**:471–6. https://doi.org/10.1111/j.1524-4725.1992.tb03307.x

32 Peris K, Fargnoli MC, Kaufmann R, Arenberger P, Bastholt L, Basset Seguin N, et al. European consensus-based interdisciplinary guideline for diagnosis and treatment of basal cell carcinoma—update 2023. *Eur J Cancer*. 2023;**192**:192. https://doi.org/10.1016/j.ejca.2023.113254

33 Gehl J, Sersa G, Matthiessen LW, Muir T, Soden D, Occhini A, et al. Updated standard operating procedures for electrochemotherapy of cutaneous tumours and skin metastases. *Acta Oncol*. 2018;**57**:874–82. https://doi.org/10.1080/0284186X.2018.1454602

34 Jamsek C, Sersa G, Bosnjak M, Groselj A. Long term response of electrochemotherapy with reduced dose of bleomycin in elderly patients with head and neck non-melanoma skin cancer. *Radiol Oncol*. 2020;**54**(1):79–85. https://doi.org/10.2478/raon-2020-0009

35 Benedik J, Ogorevc B, Brezar SK, Cemazar M, Sersa G, Groselj A. Comparison of general anesthesia and continuous sedation for electrochemotherapy of head and neck skin lesions. *Front Oncol*. 2022;**12**:1011721. https://doi.org/10.3389/fon.2022.1011721