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The Role of Electrochemotherapy in Curative Treatment of Head and Neck Cancer and Advanced Skin Cancer: A Need for New Treatment Protocols?

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Abstract. *Background/Aim: Electrochemotherapy (ECT) is a cancer treatment modality where the efficacy of a chemotherapeutic agent is enhanced by an electrical field. It is an established palliative treatment for cutaneous metastases but its role in curative treatment remains mostly undetermined. Studies have previously reported that ECT can be a safe curative treatment in both skin cancer and oral cavity cancer. The primary aim of this case study was to report the long-term results of ECT in curative treatment of four patients with skin or oral cavity cancer. The study also compares two different ECT treatment protocols. Patients and Methods: Three patients with oral cavity cancer and one patient with skin cancer were included. One patient had a primary oral tongue cancer and the others had persistent/recurrent tumors after previous treatment. They were treated with ECT either as a primary, adjuvant or salvage treatment with curative intent. The median follow-up period was 60 months. Results: There was one case of local recurrence after treatment in the follow-up period. In the other three patients, no recurrence was recorded. There was one serious adverse airway event. There was a significant difference in the bleomycin dose between the two studied protocols, especially for large tumors. Conclusion: ECT can be a safe mono-modality and adjuvant curative treatment in advanced skin cancer and primary and recurrent oral cavity cancer.*

Loco regional recurrences of squamous cell carcinoma (SCC) of the skin and the oral cavity worsens the patient's prognosis and often presents a treatment challenge. Therefore, it is crucial that the primary treatment achieves loco regional tumor control and, if the primary treatment fails, that other treatment modalities are available. Thus far, surgery and radiotherapy (RT) remain the only curative treatment modalities in SCC of the skin and oral cavity. Re-irradiation is only possible occasionally and a significant time must have passed since the primary treatment. In patients that often develop multiple primary carcinomas due to field cancerization this can be a serious limitation. The only curative treatment option in these cases of recurrent SCC is salvage surgery that often results in severe morbidity. Electrochemotherapy (ECT) is a cancer treatment modality that uses a locally applied electrical field to increase the intracellular accumulation of hydrophilic chemotherapeutic agents thereby increasing their cytotoxic effects (1, 2). Today, ECT is primarily used for treatment of cutaneous metastases of different primary tumors in accordance with the European Standard Operating Procedure of Electrochemotherapy (ESOPE) treatment protocol (3, 4). The ESOPE protocol allocates patients with cutaneous metastases to different treatment strategies based on tumor location, tumor size and number of tumors. Bleomycin can be administered either intravenously or locally whereas the other chemotherapeutic agent used, cisplatin, is for local administration only. The dose of bleomycin and cisplatin for local administration is based on the tumor volume calculated by the formula: $V=\pi ab^2/6$, where a is the longest tumor diameter and b is the longest perpendicular diameter. The dose of both chemotherapeutic agents is also reduced for larger tumor volumes in the ESOPE protocol (3, 4).

It has also been reported that ECT with intratumoral bleomycin can be a safe curative treatment of SCC in the oral cavity, oropharynx and skin with a treatment protocol that differs from the ESOPE treatment protocol (5-7). In this protocol, the treatment volume formula includes a 1 cm

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margin and a dose of 1000 IE bleomycin/cm^3 independent of the tumor volume (5-7). The local control reported in these small clinical studies was between 67 and 100%.

The potential of ECT as a mono-modality or adjuvant modality in treatments with curative intention remains, in the authors' opinion, under-investigated. In this paper, long-term follow-up in four patients treated with ECT with intratumoral bleomycin administration for treatment in oral cavity cancer and advanced skin cancer with curative intention are reported. These cases highlight the potential of ECT in different aspects of curative treatment: As a primary treatment, as an adjuvant treatment and as a salvage treatment. The bleomycin dose for the different treatment protocols was also compared.

Patients and Methods

The patients (two females, two males, mean age 55.5 years) were referred to the Örebro University Hospital for treatment. Patient and tumor characteristics are presented in Table I. Three patients with oral cavity squamous SCC and one patient with cutaneous SCC were accepted for treatment with ECT after receiving information about the treatment and the alternatives. Three of the patients had biopsy verified recurrences after earlier treatment: Surgery and, in two cases, RT (Table I). ECT was suggested as an alternative to surgery in two of the patients because the tumor borders were poorly defined (Patient 1 and 2) and in one patient because surgery would have required mandible split and free-flap reconstruction (Patient 4). Patient 3 had schizophrenia and refused RT but accepted surgery. In that patient, ECT was used for treatment of the tumor margin after resection instead of RT. The treatment decisions were made at a multidisciplinary tumor board in all cases.

All patients were treated with the same ECT treatment protocol although different electroporation systems were used (Table I). This will be called the Study Protocol (SP). In the SP bleomycin (Baxter, Halle, Germany) was administered intratumorally including a 1 cm margin of macroscopically normal tissue. The dose was 1000 IE per cm^3 of tumor volume (V) calculated by the formula: $V=\pi(a+1)\,(b+1)^2/6$ where, a is the longest tumor diameter and b is the longest perpendicular tumor diameter (5-7). The formula allows for a 1 cm treatment margin in contrast to the ESOPE Protocol ($V=\pi ab^2/6$) (3). The tumor diameters were determined using a tape measure.

After bleomycin administration electroporation was performed with either the Cliniporator (IGEA, Carpi, Italy) or the Sennex (Bionmed, Saarbrucken, Germany) electroporation systems. The tumor with at least a 1 cm margin was treated in an overlapping fashion until the whole tumor and the adequate margin was covered. Needle applicators was used in all cases and the number of applications varied between 10 and 24 related to the tumor size.

In two of the patients neck dissections were performed concurrently with ECT (Table I). RT was performed regionally in one patient after neck dissection that showed extracapsular spread (Patient 1). One patient had a recurrence after ECT treated with salvage surgery and radial free-flap reconstruction (Patient 4).

The administered bleomycin doses in the SP and the doses that would have been administered if the ESOPE protocol with intratumoral administration had been used are presented in Table I.

Table I. *Demographics, tumor classification, previous treatment, ECT treatment and outcome in the study group.*

Pat	Gender	Age (years)	Tumor location	Histology	TNM	Previous treatment	EP system	Bleomycin SP (IU)	Bleomycin ESOPE (IU)	Additional treatment	Follow-up (months)	Status	SAE	AE
1	M	71	Cheek (skin)	CSCC	rT2N2bM0	Surgery	Cliniporator	11,000+ 14,000	650+993	Local none, Regional RT	60	DWOD	None	Trismus
2	F	39	Oral cavity	OCSCC	rT2N0M0	Surgery+ RT	Cliniporator	20,180	1,715	None	61	NED	None	None
3	F	53	Oral cavity	OCSCC	T3N0M0	None	Sennex	15,000	1,004	Glossectomy and bilateral ND	60	NED	Airway	Feeding tube
4	M	59	Oral cavity	OCSCC	rT1N0M0	Surgery+ RT	Sennex	5,600	49,5	Salvage surgery	43	NED after surgery	None	Pain, trismus

Patient no 1 died after the 60-month follow-up period from an unrelated disease. Patient no. 4 had a recurrence after ECT treated with salvage surgery with no signs of recurrence afterward. CSCC: Cutaneous squamous cell carcinoma; OCSCC: oral cavity squamous cell carcinoma; EP: electroporation; SP: study protocol; IU: international units; ESOPE: European Standard Operating Procedures of Electrochemotherapy; RT: radiotherapy; ND: neck dissection; DWOD: dead without disease; NED: no evidence of disease; AE: adverse event; SAE: serious adverse event.

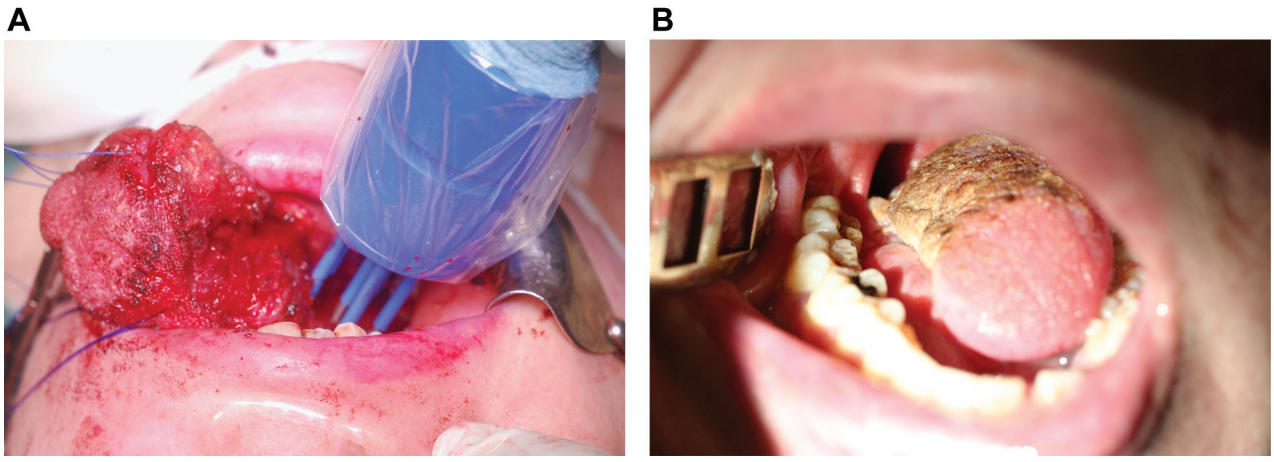

Figure 1. *Patient with a T3 tongue cancer (Patient 3). A: The surgical margin was treated with ECT with intratumoral bleomycin following subtotal hemiglossectomy. B: Three months after treatment. The nasogastric feeding tube had just been removed. The tongue mobility was good.*

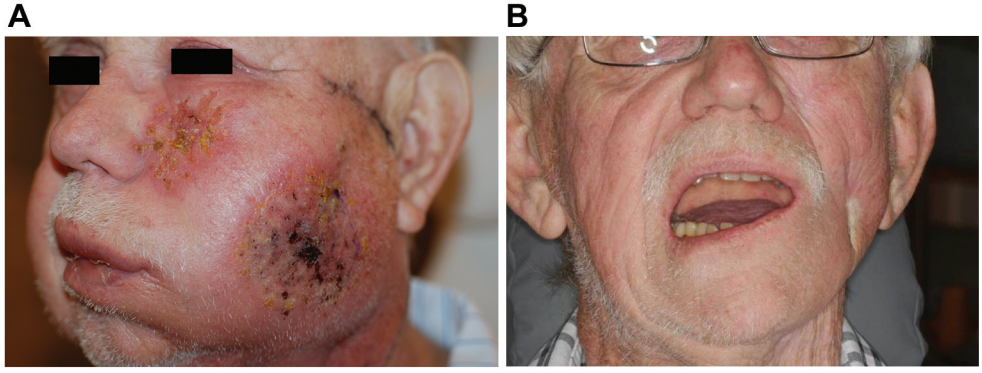

Figure 2. *Patient 1 with cutaneous squamous cell carcinoma. A: 1 week after ECT treatment. Both the primary site and the site of the positive lymph node was treated. Note the signs of toxicity in the form of swelling and erythema in the treatment area. B: Four years after treatment. The cosmetic result was good but the patient had a persistent trimus.*

All four patients have been followed clinically after treatment for a median of 60 months (mean 56 months). The follow-up has been in accordance with the recommendations in the national Swedish guidelines for head and neck cancer with clinical controls every third month for the first two years then every sixth month (8).

Results

There was one recurrence recorded in the 56-month follow-up period. Patient 4 with recurring oral cavity cancer had a local recurrence 9 months after ECT treatment and was subsequently treated with salvage surgery and radial forearm free-flap reconstruction (Table I). He is currently tumor free. No other local or regional recurrences where recorded. One patient (Patient 1) died after the follow-period from an unrelated disease.

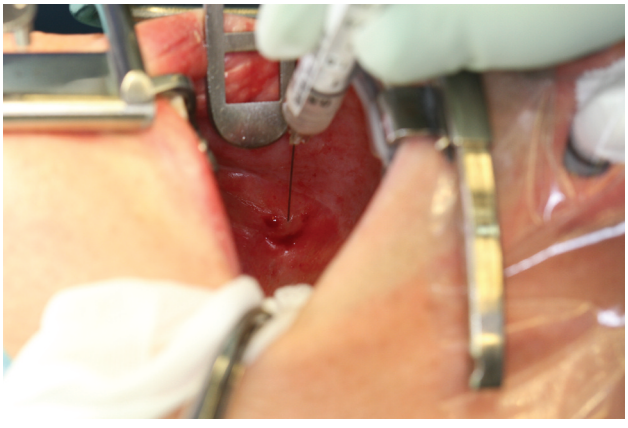

Figure 3. *Patient 4 with recurrent squamous cell carcinoma in the retromolar trigonum treated with ECT.*

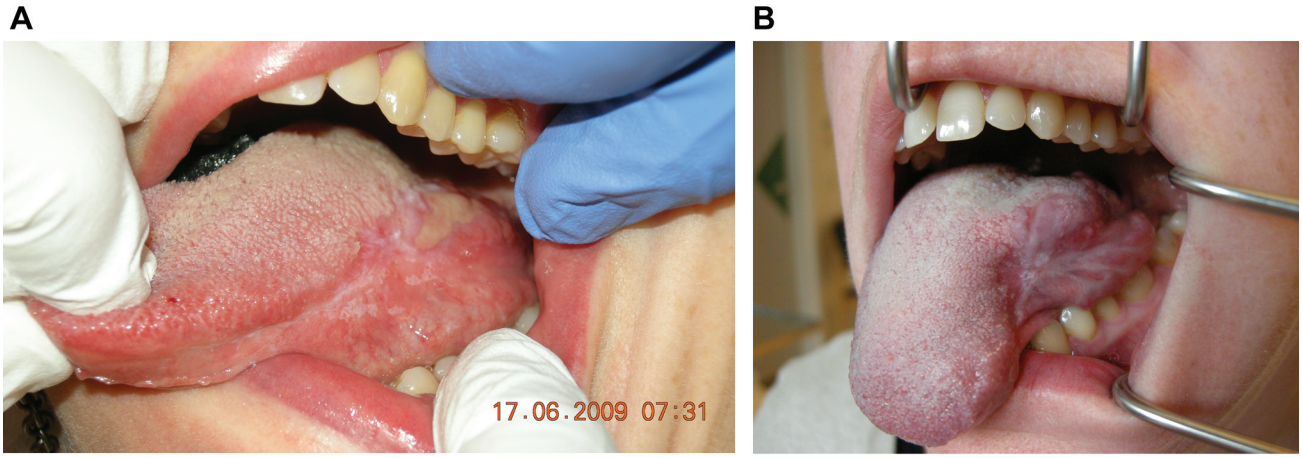

Figure 4. *Patient 2 with submucosal recurrence of tongue cancer. A: before ECT treatment. B: three years after ECT treatment, surgery would have resulted in significantly less sparing of tongue muscle.*

One serious adverse event was recorded. Patient 3 developed an airway emergency due to swelling of the tongue that required reintubation two hours after treatment (Table I, Figure 1A and B). The patient could be safely extubated two days later. There were adverse events recorded in three of the patients: A prolonged need for a feeding tube, severe postoperative pain and trismus (in two patients) (Table I).

In one case, there was a treatment malfunction where the applicator needles bended leading to an insufficient electrical field strength (Cliniporator). However, the treatment could be successfully completed by slightly changing the direction of application.

In accordance with our earlier experience healing after ECT depends on previous treatment and the treatment location. In the patient with skin cancer (Patient 1) the healing process lasted months and consisted of three phases. The first phase consisted of swelling and erythema (Figure 2A). In the second phase, there were eschar formation covering both treatment areas. In the last phase, there was remodeling eventually leading to a good cosmetic outcome (Figure 2B). There were, however, a persistent trismus leading to difficulty masticating although the patient maintained his weight (Figure 1B). In the patients with oral cavity tumors the healing process was much faster lasting weeks instead of months except in one previously irradiated patient (Patient 4, Figure 3) where there was a prolonged necrotic phase lasting almost two months. This patient also had severe pain in the necrotic phase and he also developed trismus. In patient 2, salvage surgery was considered and would, due to the mostly diffuse submucosal manifestation (Figure 4A), have included a hemiglossectomy with free-flap reconstruction. In this case ECT was organ and function-sparing since ECT treatment resulted in sparing of significantly more tissue (Figure 4B). There was no adverse event reported in this patient.

Discussion

The four reported cases, all suggest a potential role for ECT in primary treatment, as an adjuvant treatment and as salvage treatment in tumors recurring after multimodality treatment. In the first case the primary skin tumor as well as a metastatic lymph node in the parotid region was not radically resected in a previous surgery leaving very poorly defined tumor borders. Surgery would, in this case, have come with a high risk of positive margins, risk of facial nerve paralysis and poor cosmetic outcome. In this patient ECT alone provided long-term local control as well as intact facial nerve function and a good cosmetic outcome. In the patient with recurring SCC in the oral tongue after multimodality treatment ECT was a curative mono-modality salvage treatment as well as an organ and function-sparing treatment. Since the ECT treatment covered essentially the same area as the surgical alternative would have (the left half of the tongue) the selective effect of ECT towards tumor cells and tissue previously reported seems to be supported (6, 7, 9). Perhaps the most interesting case was the patient with the T3 oral tongue cancer where ECT was used instead of post-operative radiotherapy in the same session as surgery. After five years of follow-up no locoregional recurrence was detected. This application of ECT should be further investigated in a pilot study and if successful, a randomized clinical trial comparing surgery and ECT to surgery and RT should be carried out. The potential is truly enormous. If the combination of surgery and ECT for oral tongue cancer would be at least as

efficient and safe as surgery and RT these patients could be treated in just one session. There would be no need for many weeks of post-operative RT and at the same time the patient would be spared the usually severe morbidity of RT in the oral cavity. In these patients, RT could also be spared for future second primary tumors. The only case where the treatment was unsuccessful was in the patient that had a recurrence of a buccal-gingival cancer after surgery and radiotherapy. The tumor recurred less than a year after treatment and was successfully treated with salvage surgery with free-flap reconstruction. This was the same treatment that would have been performed instead of ECT in the first place and our conclusion is that the treatment strategy did not result in a need for more extensive surgery. Why did the treatment not achieve a complete response in this case? To achieve the intended effect two things are required: a sufficient concentration of the chemotherapeutic drug and a sufficient electrical field strength in the tumor tissue (10, 11). The distribution of bleomycin in the previously treated area was probably impaired leading to a too low concentration in some parts of the tumor. Maybe intravenous administration could have led to a more even distribution in all parts of the tumor. However, results from the DAHANCA 32 study with intravenous bleomycin (15.000 IU/m^2) resulted in only a 19% complete response in recurrent head and neck cancer in the 8-week follow-up period (12). There could also have been an insufficient electrical field in the pterygoid muscle space that could not be accessed by the needles. Regardless, if there is doubt about achieving a high enough bleomycin concentration or a high enough electrical field in a tumor ECT treatment should be reconsidered especially if the intention is curative. In comparison with surgery ECT seems to spare more normal tissue and it does not seem to result in permanent nerve paralysis. A drawback of ECT is that no specimen that can be examined by a pathologist is produced and thus no pT- classification of the tumor is possible.

The local toxicity of the treatment under the study protocol was significant in some of the patients. The most severe adverse event was an airway emergency in treatment of oral tongue cancer. This warrants a recommendation of either delayed extubation or a temporary tracheostomy in these patients. The healing process was prolonged in the patient with skin cancer and the functional outcome was impaired due to severe trismus in two of the patients.

The bleomycin dose administered in the study protocol was between 11.8- and 113.1-times higher than it would have been with the ESOPE protocol for two reasons. The volume formula in the study protocol differed from the ESOPE protocol by allowing for a 1 cm margin. The dose in the ESOPE protocol is also reduced with increasing tumor volumes and was 250 IU/cm^3 compared to 1,000 IU/cm^3 for all tumors in this study. This reduction in dose is probably motivated the risk of higher toxicity but seems contrary to the results published by Mali suggesting a decreased effect in larger tumors (>3 cm) (13). The higher dose in the study protocol, although achieving a very good local control in this and other studies (6, 7), comes with the price of increased local toxicity leading to trismus and a prolonged need for feeding tubes. This leads to the question: What is the lowest effective dose for treatment with curative intention? Only well designed and adequately powered clinical studies can answer that question.

This study, although small, highlights a need for more diverse treatment protocols. In palliative treatment, there should always be a trade-off between the efficacy and adverse effects. For instance, a 60% objective response can be quite acceptable in this context. However, this is not an acceptable outcome in treatments with curative intention.

Since the first clinical trial almost thirty years ago, ECT has become a safe and efficient palliative treatment alternative for cutaneous metastases of different origin (2, 14, 15). However, the potential of the treatment is, in the authors opinion, not limited to this application. In all the cases reported there was, for various reasons, a lack of good treatment alternatives. ECT is a welcome addition to the armamentarium in these special cases. But the authors opinion is that ECT could have a more prominent role in primary and adjuvant treatment of oral cavity cancer and skin cancer. To reach that position ECT must be compared to surgery and postoperative radiotherapy in randomized clinical trials and more surgeons should get involved with ECT treatment.

Conclusion

ECT have a potential for use in all aspects of curative treatment of SCC of the skin and the oral cavity: primary, adjuvant and salvage treatment. Further investigation of ECT as well as different treatment protocols in randomized controlled trials need to be examined.

Conflicts of Interest

Fredrik Landström and Stefan Kristiansson have been paid by OnMed Oncology Medical. Devices for education of future users of the Sennex electrochemotherapy system.

Authors' Contributions

All Authors have been involved in treatment and follow-up of the patients and collaborated in writing the paper.

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