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M. Gargiulo, M.D., PhD, J.M. Serra Mestre, M.D., A. Cortese, MD, DDS, D.C. Murphy, S. Parascandolo, M.D., Razzano S, M.D.

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Gargiulo M [1] M.D., PhD, , Serra Mestre JM [2] M.D., Cortese A [3] MD, DDS , Murphy DC [4] Parascandolo S [1], M.D., Razzano S [5] M.D.

Maurizio Gargiulo MD, PhD [1] mauriziomaxillo@gmail.com

Josè Maria Serra Mestre MD [2], jmserramestre@gmail.com

Antonio Cortese [3] M.D. DDS, ancortese@unisa.it

Declan C Murphy [4], murphy.declan.1994@gmail.com

Salvatore Parascandolo [1] MD, parascandolo.s@libero.it

Sergio Razzano M.D.[5] , razzanosergio@gmail.com

1. Maxillofacial Unit of Antonio Cardarelli Hospital of Naples, Italy.

2. Aesthetic, Plastic and Reconstructive Surgery Department, Hospital Quiron Barcelona; Universitat Internacional de Catalunya; and the Plastic and Reconstructive Surgery Department.

3. Maxillofacial Unit -University of Salerno, Italy

4. Norwich Medical School, University of East Anglia, Norwich, UK.

5. Department of Plastic and Reconstructive Surgery, Norfolk and Norwich University Hospital NHS Foundation Trust, Norwich, UK

Corresponding Author

Locum Consultant Plastic and Reconstructive Surgeon

Sergio Razzano M.D. razzanosergio@gmail.com

cell +39 3342274459 P.zza Muzii 11 80128, Naples Italy

Department of Plastic and Reconstructive Surgery, Norfolk and Norwich University Hospital NHS Foundation Trust, Norwich, Norfolk, NR4 7UY,UK

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Reprints:
Maurizio Gargiulo, MD, PhD, via Jannelli 190, 80131, Naples, Italy.
E-mail: mauriziomaxillo@gmail.com

Running Head:

ECT for lower lip squamous cell carcinoma.

Summary

Purpose: Electrochemotherapy (ECT) is a therapeutic approach based on the local application of electrical pulses that permeabilize cell membranes to enhance the uptake of low-permeant chemotherapeutic agents, thus increasing their cytotoxic effects.

Materials and Methods: Twenty-one patients with SCC of the lower lip were treated according to the European Standard Operating Procedures of Electrochemotherapy. Bleomycin (15,000 IU/m^2 body surface area) was administered intravenously over a 1-minute period. Eight electrical pulses (amplitude, 1000 V/cm; duration, 100 μs) were generated and delivered at a repetition frequency of 5 kHz. Changes in tumor volume were used to assess treatment response.

Results: Objective response (OR), complete response (CR), and partial response (PR) rates of 100%, 71.4%, and 28.6% respectively were demonstrated following a single session of ECT. ECT was well tolerated, and no adverse events occurred.

Conclusions: Intravenous bleomycin-based ECT is a safe and effective therapy for SCC of the lower lip. ECT improves the quality-of-life of patients by preserving the function and the aesthetic appearance of the affected area. ECT provides a therapeutic option for elderly and frail patients who, due to their state of health, are not suitable for, or refuse surgical interventions.

INTRODUCTION

Squamous cell carcinoma (SCC) is the second most common type of skin cancer (Alam M, Ratner D, 2001). The incidence of cutaneous SCC has increased over the last 15 years, possibly as a consequence of the ageing population and improvements in our ability to detect skin cancer at an early stage (Glass AG, Hoover RN. 1989; Motley R et al. 2002; 4. Rogers HW et al. 2006).

Cancer of the lip is the most common malignant lesion of the oral cavity, and approximately 90–93% of these are SCCs (Zitsch RP 3rd et al. 1995, Pohl MJ et al. 2000) Although considered the gold standard treatment option, radical surgery is sometimes unsuitable for patients due to their poor performance status or a refusal of surgery for personal, cosmetic and functional sequelae, or for fear of requiring additional and more radical surgical intervention.

Radiotherapy is also an effective treatment option for SCC of the lower lip, with comparable outcomes to surgical interventions for early staged cancers (Mali B et al, 2013). Despite radiotherapy being offerred as a primary treatment option, there may be a group of patients who are unwilling to undergo multi-staged procedures, particularly those who live in rural areas and as a result find travelling to hospitals with adequate radiotherapy services a challenge.

Several clinical studies propose electrochemotherapy (ECT) as a novel, complementary therapeutic tool to control cutaneous and subcutaneous tumors with a well-tolerated drug delivery system (Mali B et al. 2013). Chemotherapeutic drugs with low-permeability but high cytotoxicity (e.g. bleomycin and cisplatin) are administered. Following this, a series of electrical pulses into the solid tumor are applied. This enhances the uptake of chemotherapeutic agents into cells and hence increases the cytotoxic effect to the cells (Mir LM et al. 1991; Jaroszeski MJ et al. 2000; Mir LM, 2001).

Our research group has previously reported the effectiveness of ECT in the treatment of non-melanoma head and neck cutaneous and subcutaneous tumors (Gargiulo M et al. 2010; Gargiulo M et al, 2012). With this study, we pursued further investigation into the use of ECT for patients with SCC of the lower lip without evidence of cervical lymphadenopathy. We aimed to evaluate the antitumor efficacy of systemic bleomycin-based ECT in patients with SCC of the lower lip, with a long-term follow-up period.

MATERIALS AND METHODS

Patient selection

Between May 2009 and September 2015, 75 patients suffered lower lip SCC; amongst these, 21 patients with SCC of the lower lip were treated with ECT in the Maxillo-Facial Department of Antonio Cardarelli Hospital in Naples.

An electronic database was designed. It contained pre-, intra-, and post-ECT outcomes which were collected retrospectively. Written informed consent was obtained from each patient prior to treatment provision. Our inclusion criteria are as follows: patients with biopsy-confirmed SCC of the lower lip, patients with an estimated life expectancy of greater than 6 months; measurable cutaneous or mucosal tumor lesions. Patients were offered ECT as a therapeutic, palliative or neoadjuvant option based upon their current health status or due to their refusal of surgery. Recorded patient characteristics include poor general health, advanced age, cardiac disease not attributable to electrocardiac malfunction, reduced lung performance, medical comorbidities, and an unsutiability for a radical surgical intervention. Exclusion criteria included clinically manifesting cardiac arrhythmias or those with an in-situ pacemaker, interstitial lung fibrosis, epilepsy, an active infection, a past history of bleomycin hypersensitivity, kidney failure, previous treatment with bleomycin at the maximum cumulative dosage, and different anticancer therapies administered within 2 weeks of the ECT

(Mir LM et al. 2006; Campana LG et al. 2009 ; Gargiulo M et al. 2010) . Non-surgical patients were defined as those with one or more of the following characteristics: poor performance status, age greater than 85 years, cardiac deficit not related to electrical malfunction, reduced lung performance, co-morbidities preventing the use of a general anaesthesia, or those patients requiring a radical surgical procedure that they were unfit to undergo. Seven out of 21 patients had been included in our previous article (Gargiulo M et al. 2012). For each patient, the tumor size was measured using two perpendicular diameters with a caliper, and photographs were taken prior to any intervention. Computed tomography (CT) was used to determine the stage of the tumour according to the tumour, node and metastasis (TNM) classification. ECT and patient selection were based on the European Standard Operating Procedures of Electrochemotherapy (ESOPE) guidelines (Mir LM et al. 2006).

In this study, ECT was provided for a range of indications (Table1):

1. Therapeutic treatment in non-surgical patients.
2. Patients who previously underwent surgery but experienced tumour recurrence.
3. Neo-adjuvant treatment to reduce the tumor size before surgical intervention.
4. Palliative treatment, for symptomatic relief.
5. Patients who declined surgical intervention.
6. Patients who declined primary radiotherapy.

Before providing ECT, all patients had been fully informed of the specific details of their disease, about the ECT procedure and its potential risks. All patients provided written informed consent prior to treatment.

Electrochemotherapy treatment

Patients were treated under sedation with midazolam and remifentanil, and local anesthesia (2% lidocaine) was administered via a 1- to 5-mL peritumoral injection. N20 4B electrodes (IGEA S.p.A., Carpi, Italy) with linear array needles were used in all cases. Electrodes were inserted deep into the tumor and perilesional area (1-cm margins) to secure the tumor and its margins within the electrical field generated. An intravenous bolus dose (15,000 IU/m^2 body surface area) of bleomycin was injected over a 1-minute period. Eight electrical pulses (amplitude, 1000 V/cm; duration, 100 μs) were generated and delivered at a repetition frequency of 5 kHz using the Cliniporator device (IGEA S.p.A., Carpi, Italy) with hexagonal electrodes. To ensure homogeneous distribution of the drug into the tumor volume, pulses were delivered from 8 to 28 minutes after the intravenous injection (Mir LM et al. 2006; Sersa G. 2006).

Response assessment and follow-up.

Through measuring changes in tumor volume, the treatment response was evaluated, in accordance with the World Health Organization (WHO) guidelines (WHO, 1997). Treatment response was evaluated 6 weeks after the administration of ECT and was classified as follows: “Objective response” (OR), defined as any decrease in tumour volume, which was further subdivided into “complete response” (CR), when the tumor was not palpable; and “partial response” (PR), a decrease in tumor volume by >50%. “No change” was defined as an increase in tumor size of <25% or a decrease of <50% in tumor volume, and finally “progressive disease” if the tumor volume increased by ≥25%.

Patients were followed-up weekly for the first 6 weeks, and then at monthly intervals. Tumors size was measured, and photographs were taken at each follow-up appointment.

In our analysis, we describe the follow-up period at three separate time points: 6 weeks, 18 months, and the patients’ last-follow up appointment. (Table 3)

Statistical analysis

IBM SPSS statistics version 24 software was used for data analysis. Categorical variables are presented as frequencies and percentages. Follow-up length is positively skewed and is presented as a median and interquartile range (IQR), whereas age is normally distributed and is presented as means and standard deviation (SD). Outcome frequencies were calculated using basic descriptive statistics.

RESULTS

Patient demographics

Between May 2009 and September 2015, a total of 21 patients with SCC of the lower lip underwent ECT; 12 were male (57.1%) and 9 were female (42.9%). The mean age was 76.0 years (SD ±8.70) with a range from 60.0 to 91.0 years (Table 1). Non-cancerous respiratory disease constituted patients with a diagnosis of chronic obstructive pulmonary disease (n=3) or an inadequate respiratory function to undergo surgical intervention (n=1) as assessed by an independent physician. “Significant cardiovascular disease” included one, or a combination, of the following: a past medical history of ST elevated myocardial infarction (n=1), non−ST elevated myocardial infarction (n=2), coronary artery bypass surgery (n=1), stroke (n=1), current severe aortic stenosis (n=1) or bilateral carotid artery stenosis (n=1) (Table 2).

In all, 76.2% (n=16/21) of patients were treated with therapeutic intent. Five underwent ECT due to the recurrence of a previous SCC at the same location. Neo-adjuvant ECT was provided to 9.5% (2/21) of patients prior to surgery; one who had no history of previous skin cancer affecting the lip, and one who had a recurrence. Palliation was the

treatment intention in 14.3% (3/21) of patients. A refusal of surgery by the patient influenced the decision to perform ECT in 23.8% (5/21) of participants (Table 1).

Treatment response

Six weeks following ECT, an objective response (OR) was achieved in 100% of patients (21/21). In all, 71.4% (15/21) of patients experienced a CR and 28.6% (6/21) experienced a PR. No tumors showed disease progression.

After the first cycle of ECT, recurrence of the tumour was identified in 14.3% (3/21) participants. Of those who experienced recurrence, two occurred at 12 months post-ECT and one after 18 months. One patient (patient No. 3), refused additional treatment. This patient has been monitored for 49 months following the recurrence and remains in a clinically stable state with no evidence of disease progression. The other two patients (No. 9 and No. 17) underwent surgical resection of the tumour; no recurrence has been identified in either patient since.

Of the patient population undergoing ECT, 28.6% (6/21) required additional therapy. One patient required further surgery after only a PR was achieved and the tumour recurred at 12-months' follow-up (patient No. 17). In addition, surgery was indicated after an initial CR but with subsequent recurrence 18-months following ECT for one patient (patient No.12), a second course of ECT was provided following a partial response in two patients (patient No.5 and No.9), and finally two patients received a neo-adjuvant course of ECT following a PR to the first course of ECT (patient No. 2 and 6) (Table 3). Additional treatment was successful in all cases. No patients experienced further recurrence following these additional interventions.

Follow-up and response duration (Table 3)

Median follow-up length was 27 months, ranging from 18 to 74 months, with the 25th and 75th percentile equating to 21 and 49 months respectively. One patient was lost to follow-up 18 month post-ECT (patient No. 18).

At 18-month follow-up, 85.7% (18/21) patients were stable with no recurrent disease. 9.5% (2/21) experienced a recurrence of the disease: one patient refused any additional treatment and the other, whose recurrence did not occur until 18 months post-ECT, was successfully treated by surgery. One patient deceased due to an unrelated cause after 18 months' follow-up.

Three patients have died from an unrelated cause; these patients were followed up for 36, 30 and 18 months respectively post-ECT, and all showed no evidence of disease recurrence at the time of death. Of those alive (n=18), 94.4% (17/18) patients were well with no evidence of recurrent disease. Patient No. 3 experienced disease recurrence. He underwent surgical excision of the tumour with primary closure of the defect. After surgery the disease remained stable with no evidence of disease progression. At the last follow-up appointment, no instances of delayed wound healing, infection, or other minor complications were identified.

Toxicity and Other Side Effects

There was no evidence of serious ECT-related adverse effects or bleomycin-related hematologic toxicity observed in any patients. Mild erythema, limited to the tumor and surrounding tissue, appeared in 19.0% (4/21) patients after ECT. During the ECT, patients reported an unpleasant sensation due to muscle contractions associated with the electrical pulses. Some patients reported localized minor discomfort following treatment. Post-ECT pain was successfully managed with simple oral analgesia.

DISCUSSION

ECT is a key topic in surgical oncology. Both pre-clinical and clinical trials have proved its efficacy in many different tumor types that are inoperable and/or refractory to chemotherapy and radiotherapy. The antitumoral efficacy of ECT *in vitro* and *in vivo* is due to a dual mechanism involving cell apoptosis and tissue ischemia (Cemazar M et al, 2001; Mir L. 2006). The immunological-based mechanism of ECT-mediated anti-tumoral effects is under debate (Mir LM et al. 1992; Sersa G et al.1997; Mir LM, Orlowski S, 1999; Quaglino P et al. 2008). ECT-induced apoptosis has been associated with aberrant mitosis (Mir L. 2006). Within 5 minutes of applying ECT, all mitoses in the tumor are aberrant. During the 24 hours following ECT, the cells initiate repair mechanisms with mitotic division. Caspase 3−dependent atypical mitosis and a large-scale infiltration of macrophages and dendritic cells are observed, indicating tumor cell apoptosis. Experimental studies using Patent blue suggest that ECT induces ischemic necrosis of tumor cells with an anti-vascular mechanism; this is particularly useful in controlling the symptoms of bleeding nodules (Möller MG, et al, 2011). In contrast to other physical ablation technologies, ECT does not denature collagenic extracellular matrix proteins (Mir LM, et al, 1992;WHO,1997 ; Sersa Get al 1997; Mir LM, Orlowski S, 1999; Cemazar M, et al. 2001; Mir LM, et al, 2006; Sersa G. 2006 ; Mir L. 2006; Quaglino P et al. 2008; Snoj M, et al. 2009; Campana LG et al. 2009). To date, all studies of cisplatin and bleomycin-based ECT demonstrate a low toxicity profile for the chemotherapeutic agents, with minimal systemic side effects (Bloom DC, Goldfarb PM. 2005; Mir LM, et al. 2006; Punglia RS et al. 2007; Fantini F et al. 2008; Campana LG et al. 2009; Matthiessen LWet al. 2011; Muñoz MV, Ortega PG. 2011; Möller MG et al. 2011;Testori A et al. 2012 ; Campana LG, et al. 2012; Sersa G et al. 2012; Kis E et al. 2012; Mevio N et al. 2012; Curatolo P et al. 2012; Bonadies A et al. 2015; Rotunno R et al. 2016.) We did not observe any major complications in our study either. Although some patients

reported discomfort during the application of electric pulses, the treatment was well tolerated with the administration of local anesthesia. Therefore, it is advisable to use an ECT repetition frequency of 5 kHz rather than 1 kHz, as this reduced the time required to perform the treatment, which is particularly helpful when multiple lesions need to be treated during the same session. Furthermore, each electric pulse at 5 kHz generates a single contraction of the muscle underlying the area to be treated, rather than the eight contractions during a 1-minute period when a 1-kHz frequency is used.

In 2006, ESOPE showed that ECT is a valuable treatment option for up to of 80% of cutaneous and subcutaneous metastatic nodules (Mir LM et al 2006). Recent clinical studies applying the ESOPE guidelines have corroborated the effectiveness of ECT for melanoma (Quaglino P et al. 2008; Snoj M, et al. 2009; Campana LG et al. 2009; Matthiessen LW et al. 2011; Muñoz MV, Ortega PG. 2011; Möller MG et al. 2011;Testori A et al. 2012 ; Campana LG, et al. 2012) and breast cancer metastases involving the chest wall (Bloom DC, Goldfarb PM. 2005; Punglia RS et al. 2007; Campana LG et al. 2009, Muñoz MV, Ortega PG. 2011; Sersa G et al. 2012), primary skin tumors (Bloom DC, Goldfarb PM 2005; Gargiulo M et al. 2010; Gargiulo M et al, 2012; Fantini F et al. 2008; Kis E et al. 2012; Mevio N et al. 2012), and Kaposi's sarcoma (Rotunno R et al. 2016) . Our study has demonstrated that ECT is effective at treating non-melanoma head and neck cutaneous and subcutaneous tumors (Gargiulo M et al. 2010; Gargiulo M et al, 2012). ECT has been successfully used for the treatment of a rare cancer in a cosmetically sensitive area, such as the orbital margin (Statigos A et al 2015). A recent multicenter prospective non-randomized phase II trial involving a sample size of 55 patients with head and neck cancers confirmed ECT's effectiveness in providing local disease control with good functional and cosmetic outcomes. ECT has been proposed as a first-line treatment of head and neck cancers (Rotunno R et al. 2016).

The route of administration for the chemotherapy used in ECT has previously been under investigation. Two types of chemotherapy are typically used to treat mucosal head and neck cancers with ECT: bleomycin or cisplatin (Statigos A et al. 2015). Similarly there has been debate concerning whether the route by which the chemotherapy is administered affects treatment efficacy. The ESOPE guidelines advise that bleomycin should be administered using the intravenous (IV) route rather than intratumourally. As part of the ESOPE study, Marty et al (Marty G et al. 2006) demonstrated bleomycin's superiority over cisplatin for the treat of cutaneous and subcutaneous tumour nodules in patients with skin malignancies. Similarly, this study demonstrates that IV bleomycin is more effective than intratumoural, highlighted by the local tumour control rate of 88% using the IV route, compared with 73% when administered intratumourally. Most research using bleomycin ECT predominantly uses the IV route. Plaschke *et al* describe their EURECA project (Plaschke CC et al. 2017). In this study, 95% of their patient cohort received IV bleomycin. As a consequence of the current evidence, we therefore replicated the methodology of previous studies and provided bleomycin to our patients using the IV route.

The treatment of primary and recurrent SCCs of the lower lip in patients considered to be unfit for surgery remains a challenge for surgeons. In the present study, we obtained OR and CR rates of 100% and 71.4% respectively in 21 patients with SCC of the lower lip treated with a single ECT session according to the ESOPE guidelines. In our sample population, three patients underwent ECT with palliative intent, all of whom had evidence of lymphadenopathy and stage T3N1M0 cancer. One patient received ECT as neoadjuvant treatment, who had stage T4aN1M0 cancer. Rather unique to our sample population, we had five patients who refused surgery (four staged T1N0M0 and one staged T2N0M0) and subsequently received ECT therapy. In those five patients, a stable CR was achieved following a single ECT session throughout their follow-up period (55, 27, 21, 18 and 18

months). Four patients underwent a second course of ECT, two of whom received a second ECT session as neoadjuvant therapy at the time of surgery. Two additional patients underwent surgery-only following the first course of ECT.

In the present study, ECT proved to be a reliable neo-adjuvant therapy in patients with stage T3 SCC of the lower lip; higher response rates were achieved in T1-T2 tumors. The results of our study support those presented in previous studies (Bertino G et al 2016).

When evaluating the treatment response in patients with SCC, it is important to also calculate the rate of recurrences. Our study monitored all patients for 18 months or more post-ECT. Median follow-up length was 27 months, which ranged from 18 to 74 months. This length of follow-up shows the long-term efficacy of the ECT treatment for lower lip SCC and, to our knowledge, this is the longest follow-up period shown in the current literature. In our cohort, three patients presented with recurrent disease. The new lesions were diagnosed promptly and surgically treated under local anesthesia in two patients. However, one patient refused additional treatment.

Owing to the radio-responsive nature of SCCs, radiotherapy is a valid first-line treatment option for patients with early-stage N0 lip SCC (De Visscher JG, et al. 1998; Vukadinovic M et al. 2007). Radiotherapy may be considered a particularly attractive option for elderly patients; it reduces the requirement for general anaesthesia, surgical interventions or hospitalization. However, radiotherapy does have some disadvantages which may hinder its uptake by patients. The most common disadvantages include a patient's delayed wound healing, cutaneous desquamation and buccal mucositis which can take 3 to 4 weeks to heal. In addition, post-treatment complete tumour regression typically takes longer, and early biopsies may not demonstrate tumour recurrence due to atypical fibroblasts induced by radiotherapy, which can result in poorer outcomes if recurrences do occur. Finally, osteonecrosis of the jaw

is a potential radiotherapy-related complication in elderly patients and is associated with substantial treatment-induced morbidity (Thanh Pham T et al. 2015; Lai TY et al 2017).

SCC of the lower lip likely affects quality of life to a substantial degree owing to the functional and cosmetic importance of the lips in daily life. In our patient sample, no delayed wound healing or infections occurred. All lesions treated with ECT healed without any noticeable asymmetry or keloid scar formation. In particular, we noticed that the healing occurred by secondary intention which helped to maintain the continence of the mouth because of tangential scar retractions (Fig 1) However, evidence has shown that in patients will full thickness lesions, wide loss of tissue with fistula formation or labial incompetence can occur (Bertino G et al 2016). An excellent functional and cosmetic result can be appreciated following ECT, even for large tumors that otherwise would have required extensive surgery with total lip excision and free tissue transfer to reconstruct the defect (Fig 2). Unfortunately, we did not formally assess the functional and cosmetic result with any validated questionnaire. All patients were treated under local anaesthetic with or without sedation. This demonstrates an opportunity to offer an effective and validated treatment option for patients who cannot or are not willing to undergo surgical excision under general anaesthesia. This treatment improves the quality of life of patients with SCC of the lower lip, not only by conserving the anatomical integrity of the lips, but by minimizing pain and allowing patients to return to their normal activities (Bertino G et al 2016) (Fig 3).

CONCLUSION

Intravenous bleomycin-based ECT is a safe, time-efficient and effective therapeutic approach for the treatment of SCC of the lower lip. According to our findings, its main indication is for stage T1 and T2 tumors without detectable lymphadenopathy. The procedure causes no local disfigurement, nor does it alter the function of the lips. ECT preserves the

function and aesthetic appearance of the mouth. Furthermore, patients can immediately resume their daily activities after treatment. ECT is easy to perform, the learning curve is short, and the costs are reasonable, although a comprehensive cost−benefit analysis is needed to compare ECT's cost-effectiveness versus surgery. An observational study may be needed to directly compare the clinical outcomes of surgery versus ECT to treat SCC of the lower lip, which would help to determine the patient sub-group that would gain the most benefit from ECT as a first-line treatment for lower lip SCC.

Conflict of interest

No conflict of interest, either financial or other, exists. There was no funding for this study.

Author contributions

Maurizio Gargiulo was the first surgeon in all the cases reported, was involved in study concept, study design, manuscript preparation, editing and review.

Josè Serra Mestre was involved in data collection, undertook the analyses and manuscript preparation.

Antonio Cortese was involved in quality control of data, he also contributed to the manuscript review.

Declan C Murphy, was involved in data collection, interpretation, statistical analysis, manuscript editing.

Salvatore Parascandolo operated on the patients led in the interpretation of results.

Sergio Razzano was involved in data collection, operated on patients, Co-operated in the study concept, performed manuscript editing, reviewed and approved final version of the manuscript.

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Figure 1. (A) Patient No. 4, an 86-year-old woman. Lower lip squamocellular carcinoma T2N0M0. The patient refused surgery and was treated with therapeutic intent. (B) An intraoperative image displaying an example of one ECT session in this patient. (C) Stable result achieved post-ECT. Image was taken 55 months follow-up. A complete response was achieved at 6 weeks post-ECT, and disease remains stable.

Figure 2. (A) Patient No. 11, an 83-year-old man. Lower lip squamocellular carcinoma T2N0M0. Indicated for ECT following disease recurrence post-surgery. Treatment was performed with therapeutic intent. (B) An intraoperative image displaying one ECT session. (C) Image obtained 27 months post-ECT. A complete response was achieved 7 weeks post-ECT, and disease remains stable.

Figure 3. (A) Patient No. 13, a 60-year-old man. Lower lip squamocellular carcinoma T2N0M0. ECT was performed with therapeutic intent. (B) An intraoperative image of one ECT session. (C) Outcomes 21 months post-ECT. A complete response was achieved at 6 weeks, and disease remains stable.

Table 1. Baseline demographics, TNM staging, and treatment intent

Patient No	Age (years)	Sex (M/F)	Tumour type (recurrent)	TNM staging	Comorbidities	Treatment intent
1	71	M	SCC	T2N0M0	Previous lung cancer	T
2	84	F	SCC	T2N0M0	T2DM, Hypertension	N
3	80	M	SCC	T2N0M0	Hypertension, Cardiac by-pass 8 months prior	T
4	86	F	SCC	T2N0M0	Hypertension	RS + T
5	77	M	SCC	T3N1M0	None	P
6	68	M	SCC (R)	T4aN1M0	T2DM, Hypertension, Stroke	N
7	91	F	SCC	T1N0M0	Emphysema, Severe aortic stenosis	T
8	71	F	SCC(R)	T2N0M0	T2DM, Hypertension	T
9	86	M	SCC	T2N0M0	Reduced lung performance	P
10	68	F	SCC	T1N0M0	T2DM, Hypertension	RS + T
11	83	M	SCC (R)	T2N0M0	None	T
12	74	M	SCC (R)	T2N0M0	COPD, Hypertension	T
13	60	M	SCC	T1N0M0	Stroke 6 months prior	T
14	65	F	SCC	T1N0M0		RS + T
15	83	M	SCC	T2N0M0	T2DM, Hypertension, STEMI	T
16	66	F	SCC	T1N0M0	T2DM, Hypertension , NSTEMI, Emphysema	RS + T
17	80	M	SCC	T3N1M0	None	P
18	77	M	SCC (R)	T2N0M0	Alzheimer’s disease, Depression, Hip fracture	T
19	66	F	SCC	T1N0M0	T2DM, Hypertension ,	T
20	72	F	SCC	T1N0M0	T2DM, Hypertension , NSTEMI	RS + T
21	87	M	SCC	T2N0M0	None	T

F, female; M, male; SCC: dquamous cell carcinoma; R: recurrent; TNM: yumour, node, metastasis; N: neoadjuvant; T: therapeutic; RS: refused surgery; P: palliative; STEMI: ST elevated myocardial infarction; NSTEMI: Non−ST elevated myocardial infarction; T2DM: type 2 diabetes mellitus.

Table 2. Patient comorbidities

Comorbidity	No. (%)
Lung cancer	1/21 (4.8)
Non-cancerous respiratory disease	3/21 (14.3)
T2DM	8/21 (38.1)
HTN	13/21 (61.9)
Significant cardiovascular disease	7/21 (33.3)
Frailty	1/21 (4.8)
Alzheimer's disease	1/21 (4.8)
Depression	1/21 (4.8)
Hip replacement	1/21 (4.8)
Bowel cancer	1/21 (4.8)
BrCa	1/21 (4.8)
BrCa (female cohort)	1/9 (11.1)

T2DM: type 2 diabetes mellitus; HTN: hypertension; BrCa: breast cancer.

Table 3. Post-operative outcomes

Patient No.	ECT response (6 weeks post-therapy)	Tumour recurrence following first ECT (months post-ECT)	Additional Treatment required	Patient status 18-months post-therapy	Follow-up (months)	Patient's status at last follow-up appointment
1	CR	N	NONE	NR	74	NR
2	PR	N	ECT + SURGERY	NR	68	NR
3	CR	Y (12)	NONE	R	61	R
4	CR	N	NONE	NR	55	NR
5	PR*	N	ECT	NR	49	NR
6	PR	N	ECT + SURGERY	NR	49	NR
7	CR	N	NONE	NR	36	DUC
8	CR	N	NONE	NR	33	NR
9	PR*	N	ECT	NR	30	DUC
10	CR	N	NONE	NR	27	NR
11	CR	N	NONE	NR	27	NR
12	CR	Y (18)	SURGERY	R†	24	NR
13	CR	N	NONE	NR	21	NR
14	CR	N	NONE	NR	21	NR
15	CR	N	NONE	NR	18	NR
16	CR	N	NONE	NR	18	NR
17	PR	Y (12)	SURGERY	NR†	27	NR
18	PR	N	NONE	NR	LFU	NR
19	CR	N	NONE	NR	21	NR
20	CR	N	NONE	NR	18	NR
21	CR	N	NONE	DUC	18	DUC

ECT: electrochemotherapy; CR: complete response; PR: partial response; DUC: deceased from unrelated cause; N: none; NR; no recurrence; R: recurrence; LFU: lost to follow-up.

*CR was achieved following second course of ECT.

†No recurrence following surgery.