Case Series

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Surgery Section

A Case Series on Electrochemotherapy Outcomes in Nine Head and Neck Cancer Patients, Focusing on Symptoms and Tumour Size Reduction

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ABSTRACT

Introduction: Head and Neck Carcinomas (HNC) are a significant cancer burden in India and worldwide, often necessitating palliative care due to their locoregional relapse. Electrochemotherapy (ECT), a combination of electroporation and chemotherapy, has shown promise in treating cutaneous tumours and addressing the limitations of conventional therapies.

Aim: To explore the effectiveness of ECT in a palliative setting for patients with recurrent, inoperable head and neck malignancies.

Materials and Methods: This case series, conducted at Department of Head and Neck Oncology, Kolhapur Cancer Centre, Kolhapur, Maharashtra, India from January 2020 to December 2022, included nine cases that met specific inclusion criteria. Patients unsuitable for standard palliative systemic chemotherapy and with a life expectancy exceeding six months were included. ECT followed European Standard Operating Procedures of Electrochemotherapy (ESOPE) guidelines, focusing on patients with measurable cutaneous or mucosal tumour lesions and excluding contraindications. The study assessed outcomes after three treatment sessions, including bleeding, pain, discharge and tumour size, and employed Response Evaluation Criteria in Solid Tumors (RECIST) criteria to evaluate overall responses.

Results: The overall mean age of the subjects was 57.78±4.56 years, with males having a mean age of 58.4±4.2 years and females having a mean age of 56.9±4.8 years. The cases included nine individuals with the following tumour sites: Buccal mucosa 6 cases (66.67%), Parotid 1 case (11.11%), and Tongue 2 cases (22.23%). tumour-related bleeding reduced from 7 cases (77.78%) to 1 case (11.11%), and discharge decreased from 8 cases (88.89%) to 2 cases (22.22%) by the third week. Notably, 3 cases (33.33%) exhibited a complete response, another 3 cases (33.33%) demonstrated a partial response, and only 1 case (11.11%) experienced disease progression. Furthermore, 2 cases (22.22%) had stable disease.

Conclusion: The ECT demonstrated effectiveness as a palliative option for recurrent, inoperable head and neck malignancies. This approach improved health measurements, reducing symptoms such as bleeding and discharge. A substantial proportion of patients achieved favourable treatment responses.

Keywords: Chemotherapy, Oncology, Treatment outcome

INTRODUCTION

Globally, HNC comprise over 5% of all cancer cases, with squamous cell carcinomas accounting for 90% [1]. In India, they represent a significant portion of cancer cases, comprising 25% of male and 10% of female cancers [2]. Despite employing a combination of treatments, 50-60% of patients with stage III or IV HNC experience locoregional relapse, and many of them are unsuitable for further curative treatments, eventually requiring palliative care [3,4].

The ECT is a well-established approach used to treat cutaneous tumours. It combines electroporation with chemotherapy. Electroporation, a technique studied for approximately two decades, enhances the permeability of cell membranes, enabling the uptake of typically impermeable molecules like bleomycin, thereby increasing its effectiveness [5,6].

The ECT has various potential clinical applications, including palliative treatment for advanced-stage diseases, a neoadjuvant role as cytoreductive therapy, preserving organ function when standard therapies are not viable, and treating highly vascularised nodules [7,8]. The interest in ECT for HNC tumours has grown due to specific clinical challenges that can arise from the limitations or anticipated disfigurement associated with conventional therapies [9]. Numerous clinical reports have discussed the outcomes of using ECT to treat HNC tumours [10-12].

The present case series aimed to assess the effectiveness of ECT in a palliative setting for patients with recurrent, inoperable head and neck malignancies who are unsuitable candidates for standard palliative systemic chemotherapy.

MATERIALS AND METHODS

This case series, of nine cases, was conducted at the Department of Head and Neck Oncology, Kolhapur Cancer Centre, Kolhapur, Maharashtra, India, from January 2020 to December 2022. It followed the Preferred Reporting Of Case Series in Surgery (PROCESS) 2020 guidelines (prospective reporting of case series in surgery), thereby adding to the expanding evidence base on the application of ECT in cancer care [13].

A two-year study period was selected to ensure an adequate patient recruitment, treatment, and assessment timeframe. Patients of various genders and age groups were considered for participation, reflecting the diversity of the patient population affected by these challenging cancers.

Inclusion criteria: Patients 18 to 65 years of age with measurable cutaneous or mucosal tumour lesions and unsuitable for standard palliative systemic chemotherapy and with a life expectancy exceeding six months were included in the study.

Exclusion criteria: In contrast, exclusion criteria encompassed clinical contraindications such as arrhythmia, interstitial lung

fibrosis, epilepsy, active infections, known allergies to bleomycin, kidney failure, prior exposure to the maximum cumulative dosage of bleomycin, and recent administration of other anticancer therapies within two weeks of the ECT procedure.

Study Procedure

The PERMEOS electro-chemotherapy device (Model number VTP8CSC) was used. The technical aspects of ECT and patient selection were guided by the ESOPE guidelines, a well-established framework for conducting ECT procedures [11].

An indication for conventional or alternative therapies, like ECT, was devised and assessed by a multidisciplinary team consisting of maxillofacial surgeons, oncologists, radiotherapists, and radiologists. By the ESOPE protocol, ECT was administered under general anaesthesia to lessen pain and muscle spasms brought on by the procedure. The ECT procedure was carried out in a sterile operating room. Bleomycin, an anticancer medication, was manufactured in the hospital pharmacy according to standard protocols. In this way, all cancer cells that divide were killed by the concentration of bleomycin in the interstitial tissue, leaving all normal, non dividing cells unharmed [11].

Protocol of the administration: ECT with bleomycin is a targeted therapeutic approach that combines the cytotoxic effects of chemotherapy with the enhanced cellular uptake provided by electric pulses. The procedure begins with the administration of bleomycin, which can be given intravenously or intralesionally, depending on the tumour's size, location, and characteristics. For systemic administration, bleomycin is typically dosed at 15,000 IU/m^2 and infused over 5-10 minutes. In intralesional applications, the dose is adjusted based on the lesion's volume, ensuring even distribution within the tumour.

Once bleomycin was administered, electric pulses were applied to the tumour site within 8-28 minutes for intravenous dosing or immediately after intralesional injection. These pulses create temporary pores in the tumour cell membranes, allowing increased Bleomycin penetration and enhanced cytotoxicity. The pulse parameters, such as intensity and duration, were carefully calibrated according to the tumour's size and depth. Specialised electrodes, such as plate or needle types, are selected based on the tumour's morphology. The combination of bleomycin and electroporation significantly enhances local tumour control, particularly for cutaneous and subcutaneous malignancies.

Post-procedure, the patient was closely monitored for any immediate adverse effects, such as pain, local swelling, or systemic reactions. Pulmonary toxicity, although rare with intralesional administration, remains a critical consideration due to bleomycin's cumulative dose-dependent risks.

Each patient had previously undergone a combination of different treatment modalities. At their inclusion in the study, they exhibited a locoregional recurrence classified as M0 or M1 [11]. It was not amenable to curative surgical or radiation therapy and was also unsuitable for systemic treatment due to its ineffectiveness or prior utilisation.

The study evaluated the outcomes after three treatment sessions, focusing on bleeding, pain, discharge, and tumour size. Bleeding and discharge were dichotomised into "present" and "absent." tumour size was the largest size of the fungating wound in any direction in millimeters, and the pain assessment was rated based on numerical rating scale [14].

Following ECT, the study employed the Response Evaluation Criteria in Solid tumours (RECIST), version 1.1 criteria to assess the overall outcome [15]. These criteria categorised treatment responses into four distinct groups:

Complete response: Disappearance of all target lesions, with any pathological lymph nodes showing a reduction in short axis to less than 10 mm.

Partial response: Atleast a 30% decrease in the sum of diameters of target lesions.

Progressive disease: Atleast a 20% increase in the sum of diameters of target lesions.

Stable disease: Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease.

STATISTICAL ANALYSIS

Statistical analysis was conducted using Statistical Package for the Social Sciences (SPSS) software version 20.0. Categorical variables were expressed as percentages, while continuous variables were summarised as mean±Standard Deviation (SD). For the comparison of repeated measures across different time points, the Friedman test, a non parametric alternative suitable for analysing dependent groups, was employed. This approach was chosen to account for the repeated measurements obtained from the same participants at baseline, week 1, week 2, and week 3. Cochran's Q test, a non parametric statistical test, was used to evaluate differences in binary outcomes across three or more related groups or time points in a repeated measures design. A significance level of 0.05 was used for all statistical tests.

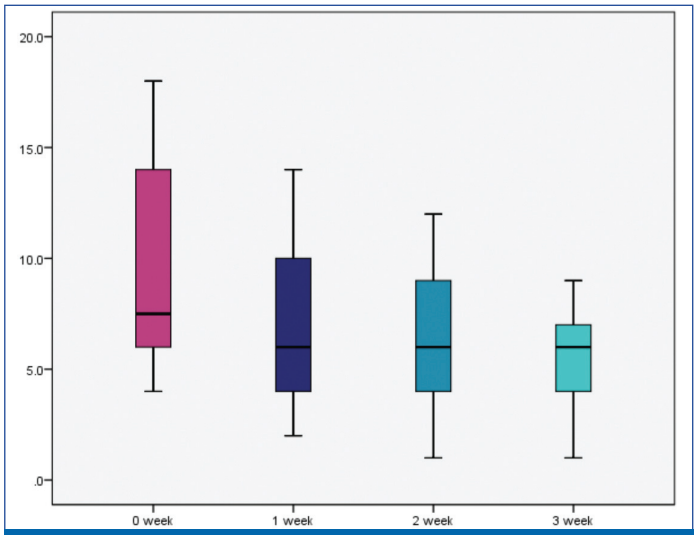
RESULTS

The authors included nine cases in the present series. The patient cohort comprising primarily males (88.88%), squamous cell carcinoma (88.88%) dominated the histopathological diagnosis, with mucoepidermoid accounting for 11.12% of cases [Table/Fig-1].

Demographic particulars	Value
Age, years (Mean±SD)	57.78±4.56
Gender, male/female {Number (%)}	8 (88.88%)/1 (11.12%)
Site, Buccal mucosa/Parotid/tongue, {Number (%)}	6 (66.67%)/1 (11.11%)/2 (22.23%)
Histopathological diagnosis, SCC/ Mucoepidermoid, {Number (%)}	8 (88.88%)/1(11.12%)

[Table/Fig-1]: Demographic particulars of the present sample.
SD: Standard deviation; SCC: Squamous cell carcinoma

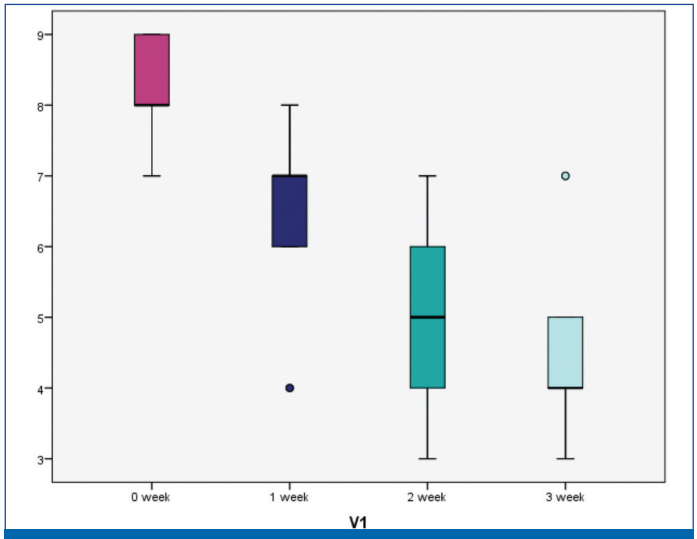
The baseline measurements for participants' tumour size showed an initial mean of 10.06±5.49. After one week of intervention, there was a noticeable shift, with the mean decreasing to 7.78±4.41. Further improvement was observed in the second week, with the mean decreasing to 6.67±3.67. By the end of the third week, the tumour size exhibited the most significant improvement, with a mean of 5.56±2.46 [Table/Fig-2], (p-value 0.0452, Cochran's Q test).



[Table/Fig-2]: Box and Whisker plot of the tumour size at different time intervals.

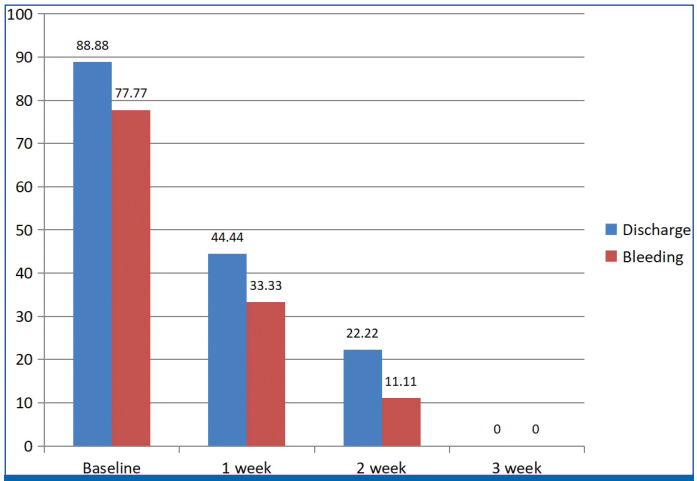
The baseline measurements for participants' pain score showed initial mean of 8.22±0.83. After one week of intervention, there was a notable decrease in the mean to 6.33±1.50. Further improvement

was observed as the study progressed into the second week, with the mean decreasing to 5.22±1.39. By the end of the third week, the pain demonstrated the most significant improvement, with a mean of 4.56±1.51 [Table/Fig-3] (p-value <0.001, Friedman test).



[Table/Fig-3]: Box and Whisker plot of the pain score at different time intervals.

Initially, 7 out of 9 cases (77.8%) experienced bleeding, which reduced to 3 cases (33.3%) after one week and just 1 case (11.1%) by the second week. Impressively, by the third week, none of the cases (0%) experienced bleeding, indicating a positive trend in symptom reduction (p=0.0016). Similarly, 8 out of nine cases (88.9%) had wound discharge initially, decreasing to 4 cases (44.4%) after one week and only 2 cases (22.2%) by the second week. Encouragingly, by the third week, none of the cases (0%) exhibited wound discharge, signifying substantial symptom improvement as the study advanced (p <0.001, Cochran's Q test) [Table/Fig-4].



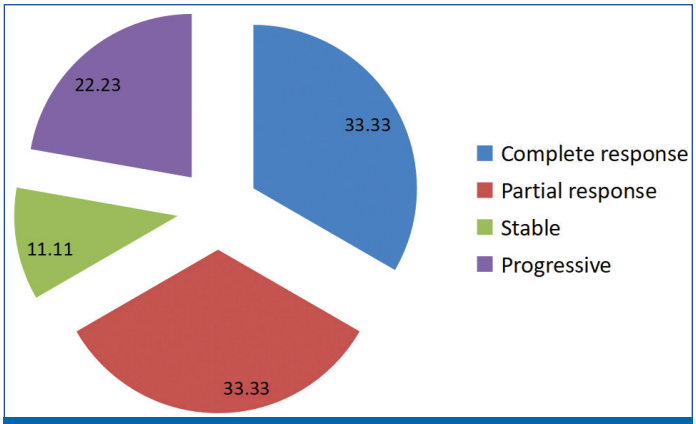
[Table/Fig-4]: Distribution of the cases based on the discharge and bleeding.

Of the nine cases studied, 3 (33.33%) had complete response, 3 (33.33%) had partial response, 1 case (11.11%) progressed, and 2 cases (22.23%) had stable disease [Table/Fig-5]. Clinical images of few cases are presented in [Table/Fig-6-8].

DISCUSSION

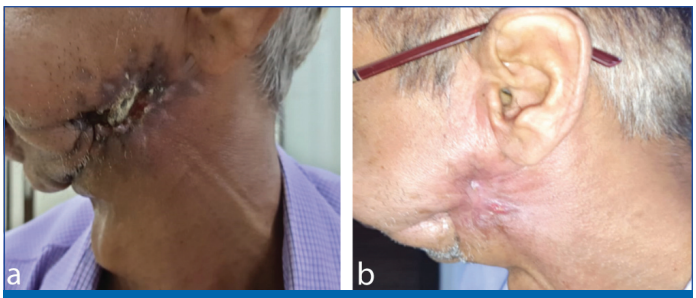
The ECT is a promising therapeutic approach for treating head and neck cancers. This innovative treatment combines the application of electrical pulses with chemotherapy agents, effectively increasing drug uptake by tumour cells [5,6]. As an evolving area of oncology, ECT continues to demonstrate its potential to enhance the quality of life and treatment outcomes for head and neck cancer patients [16-19].

This series observed a balanced distribution of complete and partial responses, aligning well with studies like that of Plaschkes J et al., which reported an overall objective response rate of 58%, and

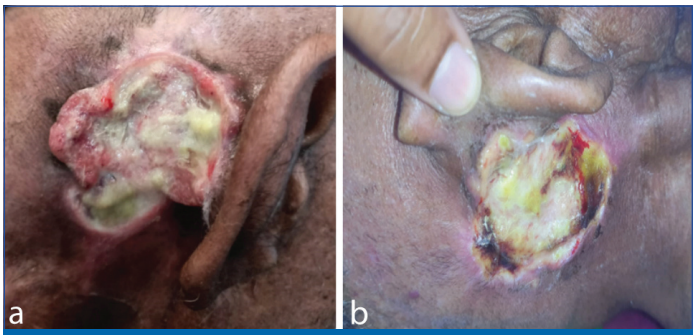


[Table/Fig-5]: Distribution based on final outcome (RECIST criteria).

[Table/Fig-6]: Fungating wound of SCC buccal mucosa. a) Baseline image; b) 2 weeks post treatment; c) 4 weeks post treatment.



[Table/Fig-7]: Fungating wound of SCC buccal mucosa. a) Baseline image; b) 4 weeks post treatment.



[Table/Fig-8]: Case of fungating wound of lymph node (Primary Buccal Mucosa). a) Baseline image; b) 4 weeks after treatment.

Campana LG et al., who reported a 38% complete response rate [9,20]. However, compared to Longo F et al., the authors complete response rate was substantially higher, as their study documented only 5% complete responses [21]. This discrepancy might be attributed to variations in patient populations, tumour types, and treatment protocols. Conversely, studies like Pichi B et al., reported an overall response rate of 100%, though only a small proportion of patients exhibited complete responses [22]. Such findings emphasise the variability in response outcomes across studies, potentially influenced by sample sizes, patient characteristics, and the extent of disease.

The present series highlighted remarkable improvements in symptoms like bleeding and wound discharge, with complete resolution by the third week. These results are consistent with Longo F et al., who also observed significant control of pain and bleeding, especially in patients with moderate symptoms prior to treatment

[21]. Similarly, Campana et al., and Pichi B et al., reported improved quality of life in terms of reduced pain and medical needs [20,22]. These findings collectively underscore the role of ECT in alleviating symptom burdens effectively.

The present study did not report any adverse effects, aligning with findings from Plaschke J et al., Campana et al., and Longo F et al., who noted minimal to mild local toxicities and no severe treatment-related complications. However, Landström FJ et al., reported some long-term issues, such as speech and sensory impairments, emphasising the need for extended follow-up to assess quality of life post-treatment [23].

Compared to Landström FJ et al., who reported a 5-year tumour-specific survival rate of 75%, and Pichi B et al., with a 12-month survival probability of 41.6%, the present study's shorter follow-up period limits direct survival comparisons [22,23]. Additionally, while other studies evaluated specific factors like tumour size, recurrence, and drug administration routes, the present study did not stratify responses based on these parameters, which may influence outcomes.

Firstly, the relatively small sample size of only nine cases may hinder the generalisability of the findings. A more extensive and more diverse sample is needed for a comprehensive assessment of ECT effectiveness in head and neck cancer patients. Secondly, the absence of a control group in this prospective case series design makes it challenging to establish causality and attribute observed improvements solely to ECT. Utilising a randomised controlled trial with a control group receiving standard palliative care would offer more robust evidence. The study's short three-week follow-up period may not capture long-term outcomes and late effects of ECT, necessitating longer-term assessments for treatment durability and potential adverse events. Furthermore, the study's focus on a specific rural hospital in India may limit the generalisability to broader populations and healthcare settings due to regional variations in healthcare practices, patient demographics, and treatment access. Lastly, the study lacks an exploration of quality-of-life aspects, such as patient-reported outcomes and psychosocial well-being, essential in palliative care.

CONCLUSION(S)

Clinical responses were encouraging, with a substantial proportion of participants showing complete or partial response to the intervention. ECT demonstrated effectiveness in reducing symptoms like bleeding and discharge and improving tumour control in recurrent, inoperable head and neck cancers.

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