Medicine

Department of Ear, Nose, Throat and Eye diseases

Harini Mahendra Prabu, 6th year, Group 5

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ELECTROPORATION APPLICATION IN HEAD AND NECK CANCER

Supervisor: Lecturer, Dr. Arnoldas Morozas

Head of Department or Clinic: Prof. Dr. Eugenijus Lesinskas

Email id: harini.mahendra@mf.stud.vu.lt

Santrauka

Aktualumas: Galvos ir kaklo vėžys vis dar laikomas viena reikšmingiausių pasaulinių sveikatos problemų, nes šiai ligai būdingas didelis recidyvų dažnis ir su tuo susijęs neįgalumas [1]. Standartiniai ligos gydymo metodai (chirurginė intervencija, radioterapija ir chemoterapija) dažnai yra riboti dėl kaupiamojo toksinio poveikio ir anatominių barjerų [2]. Šiomis nepalankiomis aplinkybėmis ypač svarbi gydymo alternatyva yra elektrochemoterapija – vietinio poveikio neterminės abliacijos metodas [3]. Taikant grįžtamąją elektroporaciją ir taip padidinant ląstelių membranų pralaidumą, elektrochemoterapija padidina chemoterapinių vaistų, tokių kaip cisplatinas ir bleomicinas, citotoksiškumą net iki 8 000 kartų [3].

ABSTRACT

Background: Head and Neck Cancer (HNC) is still considered a major global health problem because it usually presents itself with a high incidence of recurrence and associated disabilities [1]. Standard methods of treating the disease (surgical intervention, radiotherapy, and chemotherapy) usually have their limitations because of accumulated toxicity and anatomical barriers [1,2]. Electrochemotherapy or (ECT) is explained as a non-thermal local ablative technique that has emerged as a vital remedy under these adverse circumstances [3]. By utilizing reversible electroporation to increase cell membrane permeability, ECT elevates the cytotoxicity of chemotherapy drugs like cisplatin and bleomycin by up to 8,000-fold [3].

Aim: To analyse the effectiveness, reliability, and efficiency outcomes of ECT in primary, recurrent, and palliative head and neck malignancies and more primarily the research gaps [4].

Methods: A comprehensive review of clinical data (2018–2026) was conducted, focusing on Objective Response Rates (ORR) according to RECIST 1.1 criteria, Quality of Life (QoL) metrics, and safety profiles in mucosal and cutaneous HNC [5].

Results: Analysis of current trials (e.g., Insp-ECT and EURECA registries) reveals an ORR of 94.2% [7, 35, 60] for cutaneous lesions and 55–75% for mucosal recurrences [6, 8]. Tumour size 3cm and BCC histology were significant predictors of a Complete Response (CR) [4, 9]. Symptom control (bleeding and pain) was achieved in over 80% of palliative cases [10, 11], with high levels of organ and function preservation (speech/swallowing) [12, 13].

Conclusion: ECT is a highly effective, safe, and repeatable modality for the treatment of HNC [9]. It serves as a superior salvage option in previously irradiated fields and shows significant potential as an "in-situ vaccine" when combined with emerging immunotherapies [8, 14].

Keywords: Electrochemotherapy (ECT); Head and Neck Squamous Cell Carcinoma (HNSCC); Reversible Electroporation; Organ Preservation; Salvage Therapy; Bleomycin; Immunogenic Cell Death; Quality of Life.

1. INTRODUCTION

The term “head and neck cancers” (HNC) refers to a broad category of tumours from the upper aerodigestive tract, which includes the paranasal sinuses, larynx, oropharynx, oral cavity, and hypopharynx. Although the term can be considered to encompass any tumour from the head and neck, including sarcomas and lymphomas, the great majority of head and neck cancers, more than 90%, are epithelial in origin. The term HNC is considered to be synonymous with squamous cell carcinomas, which consist of squamous cells that provide a protective lining to the mouth and throat, becoming transformed into cancerous cells because of chemical irritants, such as tobacco and alcohol, and viruses mainly HPV and EBV [9, 58].

The clinical extent of HNC is precisely delineated by the World Health Organization (WHO) and the American Joint Committee on Cancer (AJCC).

Subsite	**Major Components Included**	**Clinical Relevance**
Oral Cavity	Lips, anterior 2/3 of tongue, gums, buccal mucosa, floor of mouth, and hard palate.	Often diagnosed by dentists; highest global incidence.
Pharynx	Nasopharynx (behind the nose), Oropharynx (middle throat, including tonsils and base of tongue), and Hypopharynx (lower throat).	Oropharyngeal cancer is the primary driver of the current HPV-related "epidemic”.
Larynx	Supraglottis, glottis (vocal cords), and subglottis.	Critical for voice preservation and airway management.
Paranasal Sinuses	Maxillary, ethmoid, sphenoid, and frontal sinuses, and the nasal cavity.	Often presents with late-stage symptoms due to hidden anatomical location.

Salivary Glands	Major glands: Parotid, Submandibular, Sublingual, and minor glands throughout the mucosa.	A diverse group with different histology (e.g., Adenoid Cystic Carcinoma).

Table 1: Explains the locations and clinical relevance of the cancer in these sites [8, 9].

Category	**Specific Risk Factors**	**Primary Cancer Site(s) Affected**
Lifestyle	Tobacco & Alcohol (Synergistic effect when used together)	Oral cavity, hypopharynx, larynx (voice box)
Viral Infections	Human Papillomavirus (HPV-16)	Oropharynx (tonsils, base of tongue)
	Epstein-Barr Virus (EBV)	Nasopharynx, salivary glands
Cultural Habits	Paan (Betel Quid)	Oral cavity (mouth)
Occupational	Wood, Nickel, or Synthetic dusts; Formaldehyde	Nasopharyngeal, paranasal sinuses, nasal cavity
	Asbestos	Larynx (voice box)
Environmental	Radiation Exposure	Salivary glands

Demographic	Ancestry (specifically Chinese/Asian)	Nasopharynx

Table 2: Explains the cancer location is mostly associated with specific risk factors [9, 59].

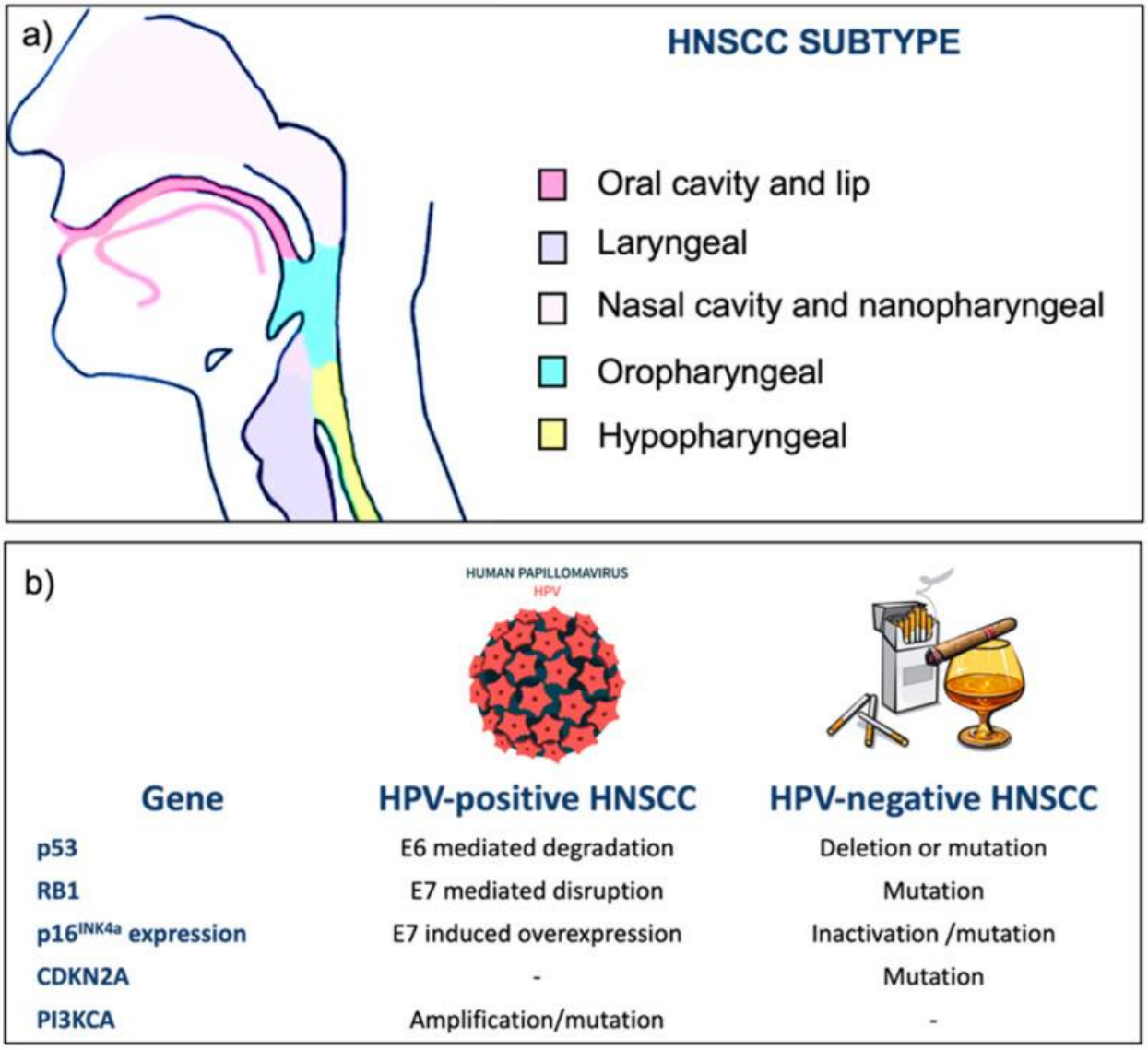


Fig. 1: Location of Subtypes and the differences between Gene and HPV positive and negative HNSCC. (Pisani et al.) [16]

As of 2026, HNC still holds its place as the seventh most common cancer type globally. The epidemiological scope of HNC has changed substantially over the past decade, with an incidence

of 940,000 new cases annually and a mortality of almost 480,000 deaths per year, mainly due to the delayed stage of diagnosis and the absence of a viable treatment option for recurrent disease [57].

Although tobacco-associated HNCs continue to decrease in some European countries, HPV positive OPSCC continues to rise, especially among younger populations. The average age at diagnosis still remains between 64 and 67 years. The highest incidence rates are seen in the 65–70-year age group, representing long-term exposure to carcinogens like tobacco and alcohol. There has been a substantial and alarming rise in cases of HNC in individuals between 40 and 60 years old. These cases are commonly related to HPV-positive oropharyngeal cancers. These patients are healthier, non smokers, and tend to have a better prognosis compared to their older counterparts [58].

HNC in young individuals is rare and includes cases related to tongue cancers, particularly in females, and those related to the nasopharynx, particularly those related to EBV. These cases tend to be without common risk factors and may be related to genetic predisposition or environmental influences [9].

One of the important aspects of the scope of HNC involves diagnostic delays. Due to the nonspecific symptoms of HNC, such as a chronic scratchy throat, voice change, and neck lump, which are often attributed to common viral illnesses. More than 60% of HNC patients are diagnosed at a locally advanced stage of disease, either Stage III or IV [11].

1.1 Current Treatment methods

Surgery is the gold standard for primary treatment, especially for oral cavity cancers. Advances in technology, such as Transoral Robotic Surgery (TORS), have enabled highly accurate resections with minimized hospital stays. However, the need for a negative microscopic margin, usually 5-10 mm, is the major drawback in conserving tissue, especially in complex anatomical locations such as near the skull base or major vascular structures [9].

Radiotherapy (RT) is used as a Primary Modality for Organ-Preserving Treatment, such as in early-stage Glottic Cancer, or as adjuvant therapy with surgery.

Systemic Therapy is usually in the form of Concurrent Chemoradiotherapy (CRT) with

Cisplatin, which enhances the sensitivity of tumour cells to Ionizing Radiation. Additionally, Immune Checkpoint Inhibitors (ICIs) targeting PD-1/PD-L1 are now considered the standard for Recurrent or Metastatic Disease, although they do not offer rapid local tumour debulking for Symptomatic Local Disease

The present scope of management is based on a multidisciplinary triad of surgical management, radiotherapy, and systemic therapy (chemotherapy and immunotherapy). However, the aim and scope of the present literature review is based on the therapeutic gap in the management of recurrent or inoperable cases [14, 20].

Surgery: Limited by functional morbidity (loss of tongue and/or larynx).

Radiation: Limited by the "Cumulative Dose" where re-irradiation is associated with a significant risk of carotid blowout.

To highlight the scope of Electroporation-based treatments as a minimally invasive and organ-preserving "Third Way" in the management of cases where traditional modalities have failed [18].

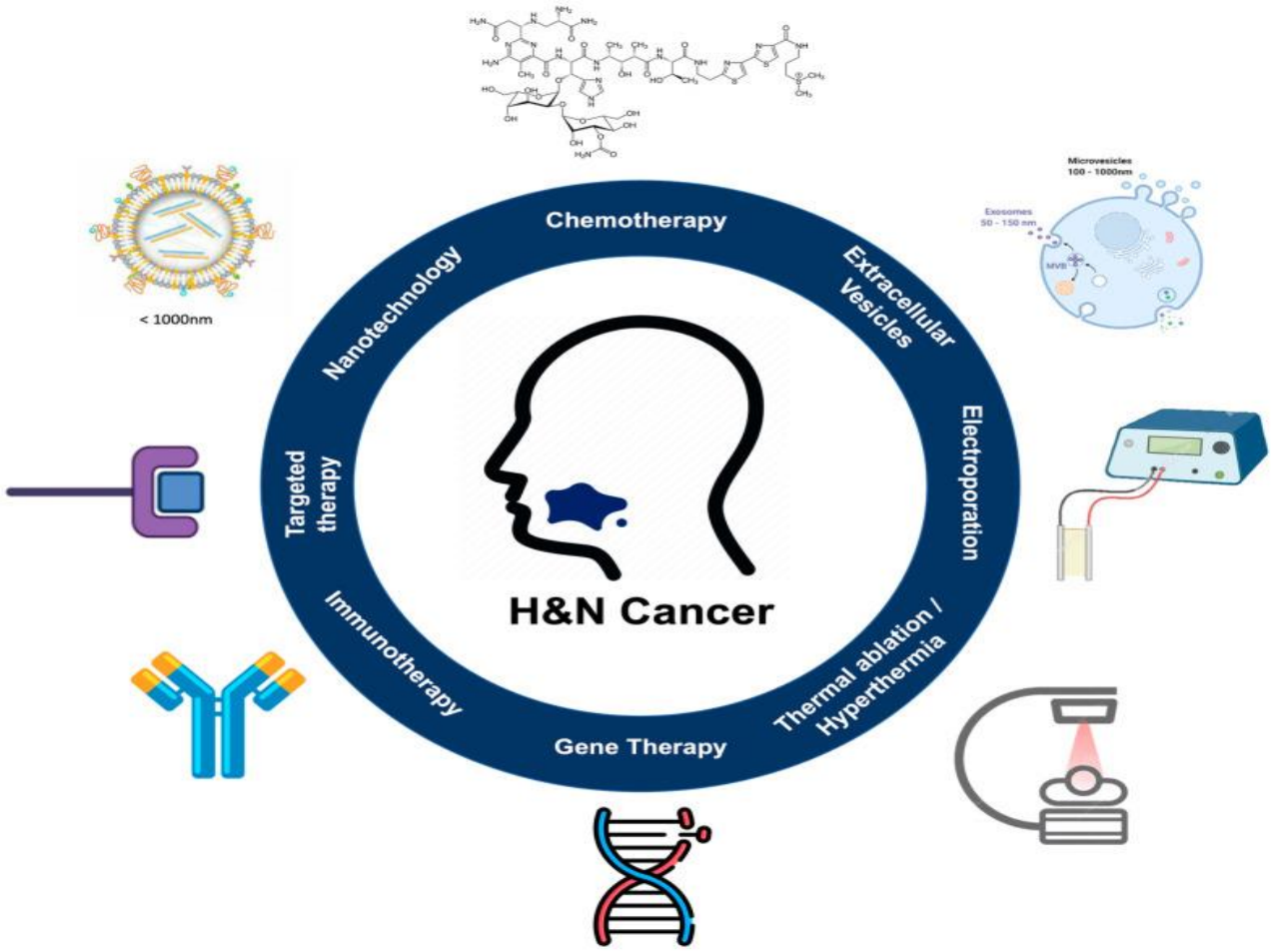


Fig.2: Summarising the existing Treatment options. (Pisani et al.) [16].

1.2 Functional and psychosocial impact

1. Dysphonia/Aphonia: Tumours in the larynx or mouth, and the tissue scarring resulting from radiotherapy, affect speech in a straightforward manner [9].
2. Deglutition (Dysphagia): This is arguably the most incapacitating long-term side effect of HNC. The pharyngeal musculature, together with the "vascular lock" of scar tissue, puts the patient at risk of chronic aspiration pneumonitis. The patient may need to change from oral feeding to PEG tube feeding [13, 14].
3. Respiration: Large glottic or subglottic tumours may require a permanent tracheostomy tube [9].

The physical inability to swallow, in conjunction with the effects of treatment-related toxicities that include mucositis and xerostomia (dry mouth), can lead to a downward spiral in nutrition. Malnutrition is present in 45% to 50% of the patient population with HNC. Loss of weight, which can be greater than 10% of the total body mass, is an independent predictor of poor QoL and increased toxicity from treatment [13].

HNC is arguably the most psychologically traumatic form of cancer to survive. The constant reminders of the disease in the physical form of scars, voice changes, and PEG tubes prevent the patient from achieving "psychological closure." [13]

Clinical depression can occur in up to 20% to 30% of the patient population with HNC.

The EORTC QLQ-H&N35 measures show that the domains of social functioning and emotional functioning in survivors of HNC are significantly compromised [11].

The treatment of Head and Neck Squamous Cell Carcinoma (HNSCC) is mostly hindered by a “therapeutic ceiling”; a dose beyond which the toxicity of the treatment exceeds its potential benefit, especially in the recurrent disease. In a patient who has already undergone radical resection or high-dose radiotherapy, the surgical site becomes a “frozen neck”, a dense, fibrotic mass where the normal planes of anatomy are lost [11, 14]:

1. Technical Risk includes Dissection near the carotid artery or cranial nerves with the risk of haemorrhage or permanent neurological damage.
2. Functional Loss: In “mutilating” surgery, which leads to the loss of the larynx, tongue, or part of the jaw, resulting in a severe loss of Quality of Life (QoL).
3. Radiotherapy: The “lifetime dose” of a healthy tissue has a finite limit beyond which it cannot be protected from irreversible damage. Most patients receive the maximal dose during their initial treatment. If the tumour recurs in the same site, re-irradiation is often not feasible because the adjacent structures such as the mandible have already attained their safe limit [14].
4. Severe Late Toxicities: The tendency to "overcome" the dose will inevitably increase the risk of life-threatening side effects, such as Osteoradionecrosis (ORN) of the jaw and Carotid Blowout Syndrome (CBS) [14, 20].

5 Pharmacological Barriers: Hypovascularity and Resistance Systemic chemotherapy and immunotherapy are hindered by significant delivery difficulties in the head and neck district after prior treatments [18].

6 The "Delivery Gap": Fibrosis resulting from prior radiation treatment decreases the blood supply (hypovascularity) to the tumour. This implies that, regardless of the drug's efficacy, it will not penetrate the "centre" of the tumour because the "vascular highways" are gone [20].

7 Acquired Resistance: Tumours that relapse after the initial chemoradiotherapy are composed of "radio-resistant" and "chemo-resistant" cell populations that have survived the first treatment and are consequently not affected by the second treatment [20].

The lack of efficacy of the “standard triad” in recurrent or inoperable patients has catalysed a transition towards biophysical approaches that focus on the importance of the structural and functional integrity of the head and neck region. Electrochemotherapy (ECT) has been identified as a leading organ-preserving therapy (OPT) that targets the “therapeutic gap” created by surgery and radiation [8, 9].

1.3 What is Electrochemotherapy?

Electrochemotherapy is a local-regional treatment that involves the administration of a low dose, non-permeant cytotoxic agent, either Bleomycin or Cisplatin. Although these drugs have low potency under normal conditions due to the inability of the drugs to cross the cell membrane, the application of electric pulses enables the drugs to reach their intracellular targets with unprecedented efficiency. "Electroporation is a biophysical process in which the lipid double layer of the cell membrane is subjected to a high-intensity electric field." The high-intensity electric field induces a "dielectric breakdown" in the membrane, creating aqueous nanopores that allow large, hydrophilic, or highly charged molecules, e.g., drugs or DNA, to enter the cytoplasm, which would otherwise be impossible under normal physiological conditions [8, 9, 10].

<u>Biophysical mechanism</u>

The main principle behind ECT is the concept of reversible electroporation. The lipid bilayer of the cell membrane is a very effective insulator under normal conditions and maintains a stable transmembrane potential [30].

There are two types of electroporation: reversible and irreversible.

Reversible Electroporation (RE): The electric pulses are of short duration. Once the electric field is removed, the cell membrane re-seals itself. This is the principle on which Electrochemotherapy is based, as the cell can survive the "shocks" but is destroyed from the inside by the drug Bleomycin [56].

Irreversible Electroporation (IRE): The electric pulses are of long duration, causing the pores to be permanent, thereby leading to the complete loss of homeostasis in the cell and its death. This is the method by which "cold" tumour ablation is achieved, with no need for drugs [29].

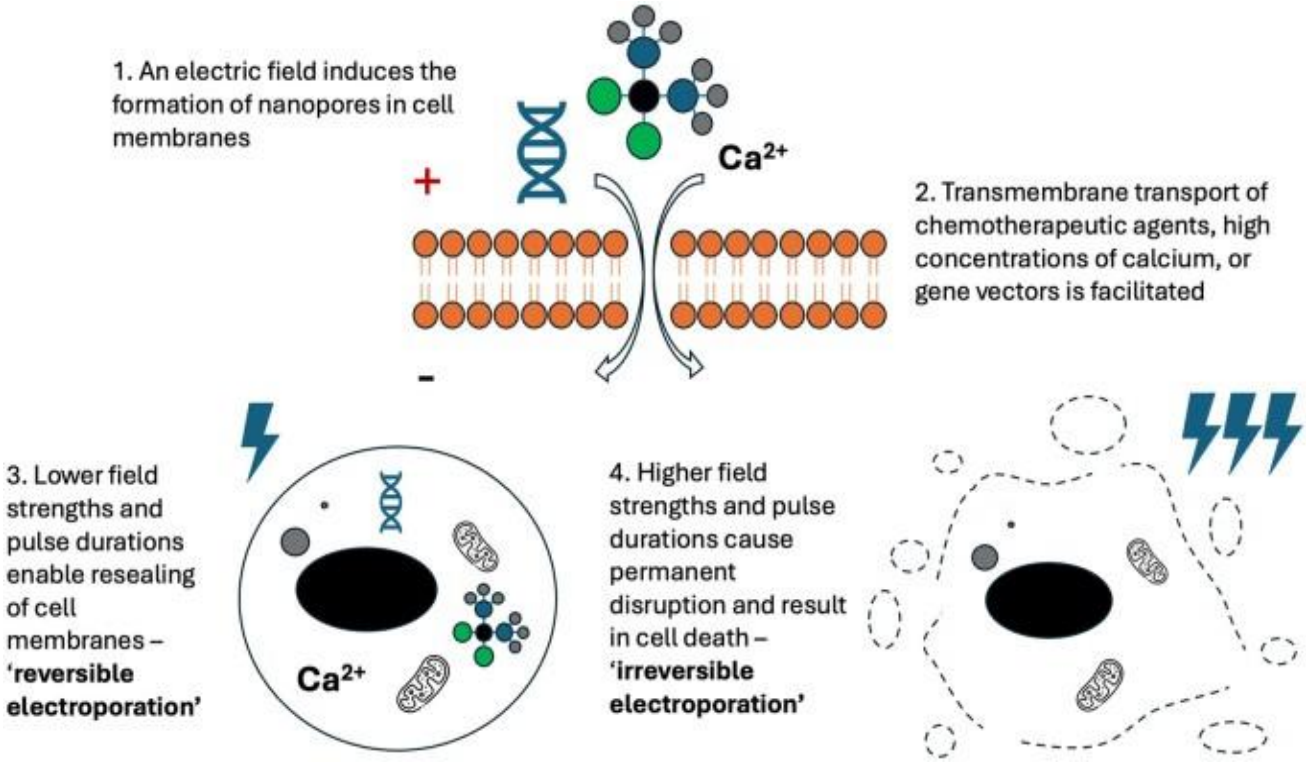
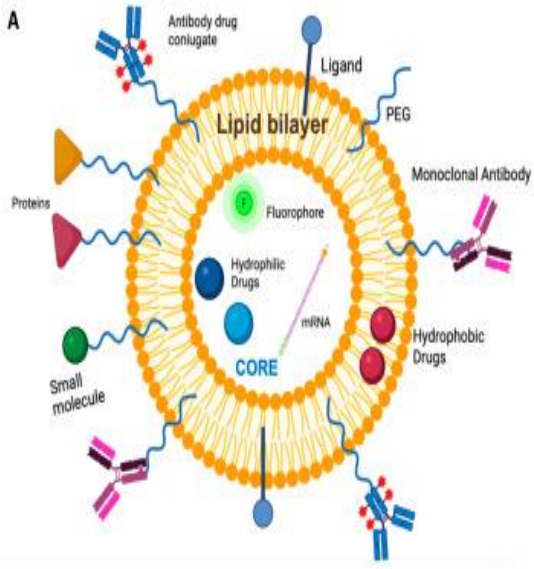


Fig. 3: Demonstrates the two types of Electroporation methods (Taha Shiwani, 2025 et al.)

The process involves several different steps [9, 55, 56]:

- Induction of Transmembrane Potential: Each cell has a resting membrane potential. However, with the application of an external electric field, extra potential is generated.
- Threshold Achievement: When this potential is achieved at a critical value (200-400 mV), the electrostatic repulsive force between the lipid groups can overcome the surface tension of the membrane.

- Pore Formation: The lipid groups are re-aligned in a direction that is stable, forming water-filled channels known as pores.
- Nanopore Formation: If an external electric field is applied, it exceeds the dielectric strength of the cell membrane. This causes a temporary change in the orientation of the lipid molecules, leading to the formation of "nanopores."
- Increased Permeability: The nanopores behave like a channel for the diffusion of large, hydrophilic molecules like Bleomycin across the lipid bilayer. Once the molecule is inside the cell, the cytotoxicity of the molecule increases by as much as 8,000 times because it can induce double-stranded DNA breaks freely.
- Membrane Resealing: The cell membrane can reseal itself once the external electric field is removed. The cell will remain alive long enough for the drug to induce apoptosis, a much "cleaner" process than the necrotic death caused by thermal therapy, depending on the strength and duration of the electric pulses.



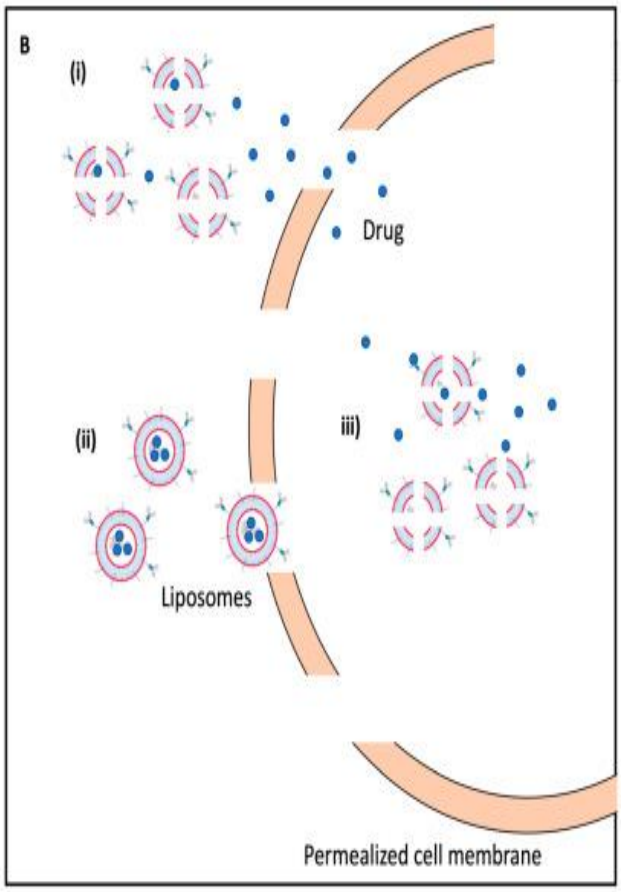


Fig. 4: (A) Schematic diagram depicting graphic illustration of liposome containing hydrophilic molecules within and hydrophobic molecules in lipid layer having surface functionalization to facilitate selective targeting; (B) Effects of electric pulse treatment on liposomes and cell membrane (i) Liposomes permeabilization with drug release near cell membrane; (ii) Liposomes-mediated entry through the permeabilized cell membrane; (iii) Liposomes permeabilization with intracellular drug release. (Pisani et al.) [16].

1.4 Need For These Organ-Preserving Therapies:

The limitations of conventional therapies (surgery and radiation), electroporation-based therapies fulfil three important clinical needs:

- Anatomical Preservation: Conventional surgery involves the removal of the tumour and a "safety margin" of normal tissue. In the head and neck area, this may involve the removal of the tongue or the nerve. ECT is a non-thermal and tissue-selective process; it affects cell membranes but preserves the "scaffolding" (collagen and elastin). This enables the surgeon to treat tumours in direct contact with major blood vessels or nerves without damaging them [18].
- Overcoming the "Frozen Neck": In recurrent disease, where there is poor vascularity due to previous radiation (hypovascularity), systemic therapies cannot reach the tumour. ECT overcomes this by opening "gates" for the drug, and the "Vascular Lock" ensures that the drug remains in the tumour's bed and is not washed out [14, 55].
- Repeatability: Unlike radiation therapy, electroporation does not cause cumulative tissue damage. It can be administered repeatedly in the same region, allowing the "inoperable" patient another chance [8, 20].

2. Materials and Methods

2.1 Literature Search Strategy

A narrative literature search was conducted to identify relevant clinical studies evaluating the efficacy and safety of Electrochemotherapy (ECT) in head and neck cancer (HNC) [8, 9].

Information Sources and Databases

The primary search was performed across the following electronic databases:

- PubMed/MEDLINE: For high-impact peer-reviewed clinical trials and biomedical literature.
- Scopus / Elsevier: For comprehensive coverage of oncology and medical physics.
- Google Scholar: As a secondary source to capture recent citations.

2. 2 Search Terms and Boolean Strategy

The search utilized a combination of Medical Subject Headings (MeSH) and free-text keywords. The following Boolean string was adapted for each database:

("Electrochemotherapy" OR "Reversible Electroporation" OR "Electroporation-based therapy") AND ("Head and Neck Neoplasms" OR "HNSCC" OR "Oral Cancer" OR "Oropharynx" OR "Larynx") AND ("Bleomycin" OR "Cisplatin") Search Filter Applied:

- Date Range: 2008 – 2026
- Language: English
- Study Type: Clinical trials, case-control studies, cohort studies, and systematic reviews.

2. 3 Inclusion and Exclusion Criteria

To maintain the focus on organ-preserving outcomes for HNC, strict eligibility criteria were applied.

Category	Inclusion Criteria	Exclusion Criteria
Population	Adults (≥18) with primary or recurrent HNSCC, BCC, or Salivary Gland Cancer.	Paediatric cases or non-HNC malignancies (e.g., breast, liver).
Intervention	Reversible Electroporation combined with Bleomycin or Cisplatin.	Irreversible Electroporation (IRE) or thermal ablation (Laser/RFA).
Cancer Site	Mucosal HNC (oral cavity, pharynx, larynx) and cutaneous HN metastases.	Central Nervous System (Brain) or Ocular tumours.
Study Design	Prospective trials, retrospective cohorts, and systematic reviews.	Single-patient case reports or animal/in-vitro studies.
Outcome	Must report Objective Response Rate (ORR) or Quality of Life (QoL).	Studies lacking clinical outcome data.

Table 3: Summarizes the Inclusion and Exclusion criteria

2. 4 Study Selection and Data Extraction

The selection process was conducted in three stages:

1 Title and Abstract Screening: Initial removal of duplicates and irrelevant topics.
2 Full-Text Review: Evaluation of the remaining papers against the Inclusion/Exclusion criteria.

Assessment of Evidence (2020–2026 Context): A significant "Research Gap" exists because the vast majority of current literature (75% of identified studies) consists of small-scale prospective cohorts (N < 30) or retrospective analyses [60, 61].

3. BIOLOGY

Electrochemotherapy is not only a pharmacological triumph in head and neck oncology but also represents a biophysical event. Here, we examine the characteristics of dielectrics associated with the cell membrane and explain how manipulation of those dielectric properties results in a "window" for delivery of drugs without compromising the "scaffold" in the neck. The plasma membrane is a semi-permeable lipid bilayer structure about 5 to 10nm thick that must maintain the electrochemical gradient. Bioelectrically speaking, it acts as a biological capacitor.

Resting Transmembrane Potential: There is always an electrical gradient maintained within cells of –70 mV [9, 18].

Induced Potential (ITV): An externally imposed electric field can induce an electrical polarization effect within the cell. In accordance with Schwan's equation, the induced potential is at its maximum at the cell poles toward the electrode.

Dielectric Breakdown: The electrical repulsion of the lipids occurs as soon as the combined induced potential reaches 200-400 mV due to the electrical surface tension of the membrane.

- 200-400mV, the electrical repulsive forces between lipid headgroups exceed the membrane's surface tension, leading to the formation of aqueous nanopores. [9]

Feature	Reversible Electroporation (RE)	Irreversible Electroporation (IRE)

Definition	Temporary permeabilization; pores reseal after the field is removed.	Permanent membrane rupture; leads to immediate loss of homeostasis.
Field Strength	Lower (400-800 V/cm typically used in ECT).	Higher (1000 V/cm typically).
Cell Fate	Cell survives the "shock" to process internalized drugs .	Cell dies directly from necrotic or apoptotic pathways .
Clinical Use	Electrochemotherapy (ECT).	Non-thermal ablation (e.g., in prostate/liver).

Table 4: Portrays the differences in the features of Reversible and Irreversible Electroporation [55, 56]

3.1 Pharmacologic Synergy: DNA Damage Mechanisms

ECT acts as a potentiation factor in that such drugs do not possess the ability to penetrate through the hydrophobic nature of the lipid bilayer. Thus, ECT converts "non-permeant" drugs into highly potent ones by allowing them to access the nucleus.

- ➔ Bleomycin: Is a large molecule with hydrophilic properties that do not permit the molecule to penetrate through the lipid bilayer easily. When using electroporation, its cytotoxicity increases 300-700 times. After penetrating cells, it acts as a "mini enzyme," cleaving double strands of DNA to give pseudoapoptosis mitotic cell death [9, 56].
- ➔ Cisplatin: Though having moderate permeability, electroporation increases its penetration 10-70 times. It causes intrastrand DNA cross-linking, thus, preventing replication and initiating apoptosis.
- ★ Vascular Dynamics: Lock and Disruption: Arguably, the most vital contribution of ECT to an "organ-preserving" method would be its action on the vascular bed [55].
- ★ Vascular Lock (Instantaneous): The pulses act instantaneously, constricting micro vessels. Thus, there is a "locking up" of the drug within the tumour for 10 minutes. During this time, maximum drug diffusion occurs without side effects [55].

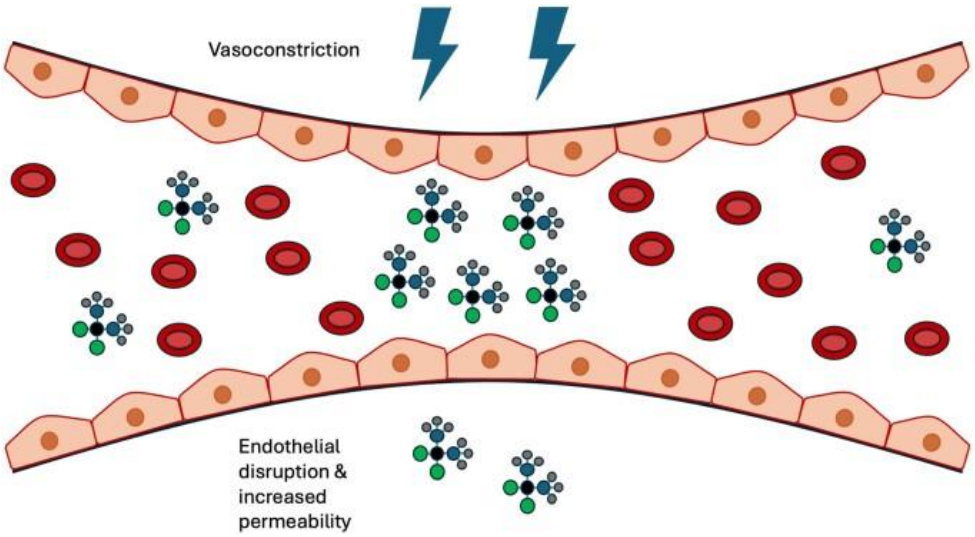


Fig. 5: "A depiction of the "vascular lock" phenomenon, whereby the electric field applied during ECT causes vasoconstriction that reduces tumour blood flow and decreases drug washout" (Taha Shiwani, 2025 et al.)

- ★ Delayed Vascular Disruption: Tumour vascular endothelial cells are also electroporated. They accumulate high levels of the drug and are killed. The blood supply to the tumour becomes ischemic without damaging the collagenous structure of major vessels [61].

Immunogenic Cell Death ("In-situ vaccine").

- ★ New oncology: ECT is not only a local destruction of a tumour, also involves the activation of immune response and upon cell death, they emit DAMPs [55]:

Calreticulin (CRT) – comes to the cell surface as a signal to phagocytes "Eat me".

HMGB1 + ATP – emitted as danger and find me signals for dendritic cells [55].

- ★ Systemic effect: Dendritic cells activate cytotoxic T-cells, inducing the "Abscopal Effect" – shrinking of untreated metastases far from ECT target site [47].

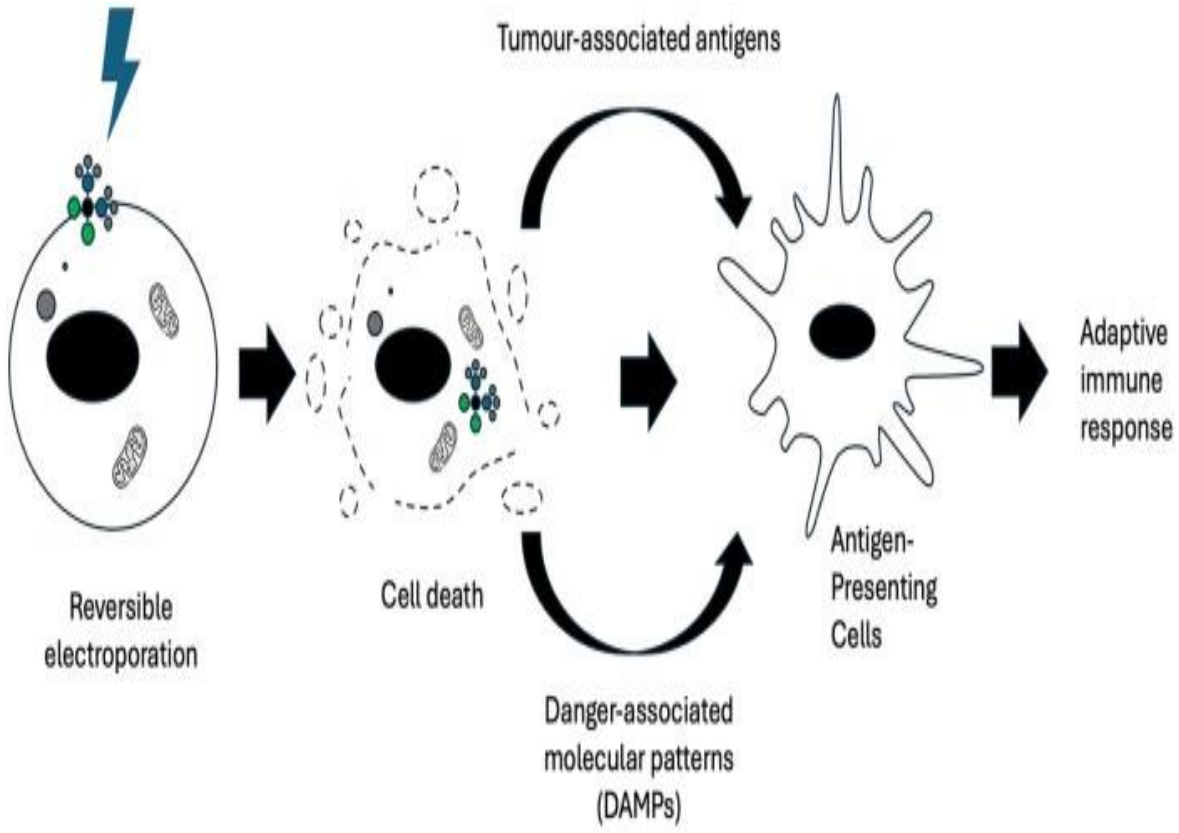


Fig. 6: "A summary of the process by which ECT establishes an anti-tumoural immune response". (Taha Shiwani, 2025 et al.)

3. 2 STANDARD PHARMACOLOGIC AGENTS:

At present, only two cytotoxic agents have been proven to be effective in ECT as a result of their high intrinsic toxicity once inside the cell and their inability to pass through intact cell membranes. The drugs are not used for their systemic effect, but for their local potential once the cell membrane is "unlocked. Bleomycin is the most commonly used agent in head and neck ECT. It is a hydrophilic antibiotic that causes cell death by producing single- and double-strand DNA breaks. Its "speciality" is its high cytotoxicity (double-strand DNA breaks) combined with its inability to enter the cell [9, 56].

- ★ **Bleomycin**: The Primary choice and DNA scissor.

Administration Routes:

- ➔ IV Administration: Recommended for large tumours or for those that are multiple in number. Standard dose is 15,000 IU/m^2 (rapid IV infusion, approx. 30-60s) [56].
- ➔ IT Administration: Used for small tumours only and for situations where systemic toxicity should be avoided. Dosage is evaluated by volume of Tumour; 1,000 IU/cm^3 [8].

The "Treatment Window":

For IV administration, pulses must be delivered between 8 and 28 minutes post-injection, coinciding with peak drug concentration in the tumour extracellular space.

For IT administration, pulses are applied immediately (within 1–10 minutes) [8].

- ★ **Cisplatin**: An Alternative with Precision

It is used when Bleomycin cannot be prescribed (i.e., for people with lung fibrosis or who have had prior high doses of Bleomycin) [8, 20].

- ➔ Method of Administration: Mostly Intratumoral (IT).

Dosage: 2mg/cm^3 (saline diluted) [8, 20].

General Systemic Treatment: Systemic administration of Cisplatin is not advised for use in ECT since it will reach toxic amounts before reaching sufficient concentrations within the tumours [18].

Feature	Bleomycin (Standard)	Cisplatin (Alternative)
Cytotoxicity Increase	up to 8,000-fold	10–80 fold
Best Route	Intravenous (IV)	Intratumoral (IT)
Indication	Multiple/Deep-seated tumours	Solitary/Superficial tumours

Limiting Toxicity	Pulmonary fibrosis (cumulative)	Nephrotoxicity (rare in IT)
HPV Sensitivity	Consistent response	Higher in HPV+ HNSCC

Table 5: Explains the features of Bleomycin and Cisplatin [8, 56]

Mechanism: After nanopores are formed by electroporation, Bleomycin becomes 300-700 times more active on most cells and up to 8,000 times on certain types of mucosal squamous cells.

Selection: It is considered the "gold standard" for squamous carcinoma of the head and neck (HNSCC) [9].

Cisplatin: The Intratumoral Specialist

Cisplatin is a platinum compound. Even though it can be absorbed into cells slowly through passive diffusion, ECT increases its absorption rate by 10-80 times [8, 20].

Selection: Used in small isolated nodules or if Bleomycin cannot be used in a patient because of their lung fibrosis or past maximum dose treatment.

Methods of Delivery: Deciding upon using Intravenous (IV) or Intratumoral (IT) delivery depends on the number and size of the tumours [8, 20].

Feature	Intravenous (IV) Delivery	Intratumoral (IT) Delivery
Dose	15,000 IU/m^2 (Bolus)	1,000 IU/cm^3 of tumour
Preferred For	Multiple nodules, large tumours (>3cm), or deep-seated mucosal lesions.	Solitary, small nodules (<2cm) or cutaneous metastases.
Timing	Pulses must be delivered in the 8-28 minute "window."	Pulses delivered immediately (1-10 minutes).
Advantage	Uniform drug distribution via the bloodstream, even in irregular tumour shapes.	Higher local concentration with near-zero systemic toxicity.

Table 6: Summarizes the difference in features of the two modes of Drug delivery [8, 9, 20] .

4. Technical Specifications

4. 1 The "Recipe for the Electrical Stimulation"

The waves do not consist of "random shocks" but precisely calibrated waveforms which will achieve permeabilization without heating up the tissues (non-thermal treatment).

Voltage (Electric Field): Typically ranges from 1000 – 1300 V/cm (depends on electrode separation) [56].

Duration of the Pulse: Duration of each individual pulse lasts precisely 100µs. It allows achieving polarization of the membranes without causing thermal effects [9, 18].

Frequency: Clinical frequencies range from 5 kHz (high frequency) to 1 Hz (low frequency). 5 kHz is preferable due to lesser muscle contractions [9, 56].

A Series of Pulses: 8 rectangular pulses in a row [56].

4. 2 Equipment: The Electrodes

The choice of electrode determines the "shape" of the electric field [8, 18].

- ➔ Plate Electrodes: Two parallel metal plates. Used for very superficial skin lesions.
- ➔ Needle Electrodes: Inserted directly into the tumour.
- ❖ Linear Array: Two rows of needles. Good for flat, wide lesions.
- ❖ Hexagonal Array: Six needles in a circle with one in the middle. This creates a highly uniform field and is the preferred choice for deep-seated head and neck tumours to ensure the entire volume is treated [18, 56].

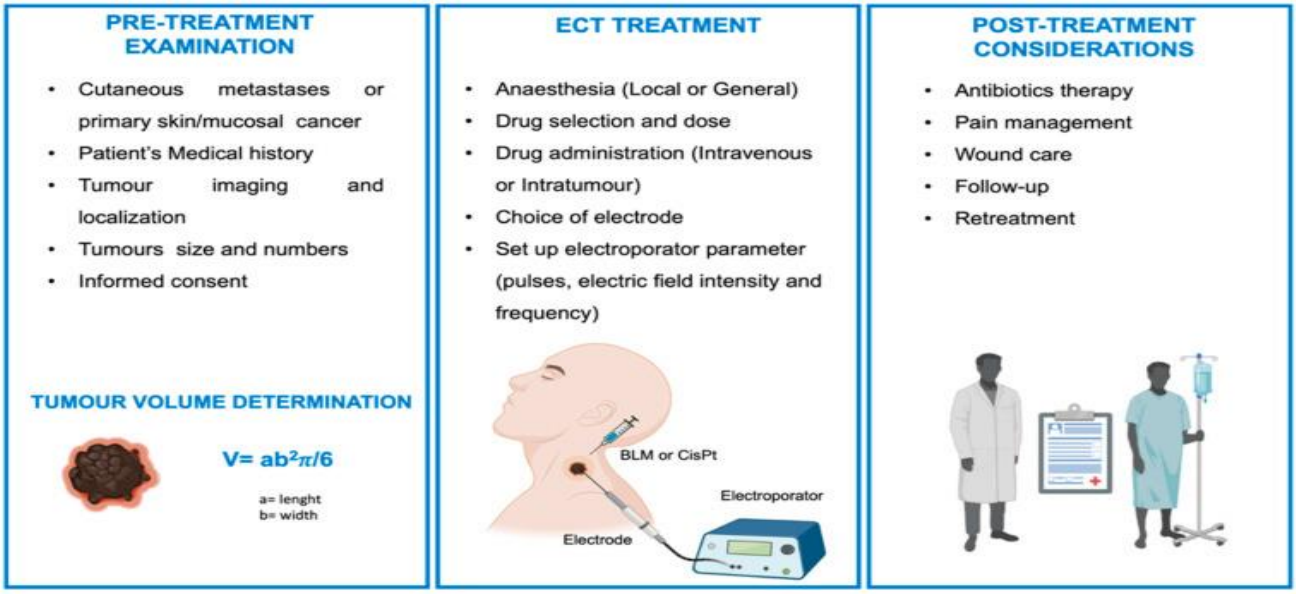


Fig. 7: "Overview of Standard Operating Procedure (SOP) for Electrochemotherapy (ECT)" (Pisani et al.) [16].

4.3 Anaesthesia and Patient Monitoring

ECT induces muscle contractions (direct stimulation of the neuromuscular junction) and can be painful.

- ❖ General Anaesthesia: Recommended for all head and neck mucosal cases. It allows for total muscle relaxation (using neuromuscular blockers like Mivacurium) to prevent patient movement during pulse delivery near vital structures like the carotid artery [8, 39].
- ❖ Sedation: Can be used for small cutaneous lesions [8].
- ❖ Monitoring: Standard ASA monitoring is required (ECG, SpO2 , BP). Special attention is paid to ECG synchronization. To prevent triggering an arrhythmia, the pulse generator can be synchronized to deliver pulses during the refractory period (the R-wave) of the heart cycle [11].

4.4 Selection Criteria of Patient and Tumour

Tumour Size: There is a 'cut-off' size of 3 cm based on studies. The CR rate is much higher (59.5%) for tumours less than 3 cm in size as opposed to those greater than 3 cm (33.3%). ECT treatment plans for tumours >3 cm generally involve several treatments [8, 9].

Histotypes: Although rare in other histotypes, ECT is highly effective on BCC and ACC tumours because of their slow-growing nature and defined borders [20].

Contraindications: ECT treatment is not recommended to be administered to patients suffering from pacemakers near the site of application, severe pulmonary fibrosis (with Bleomycin), or epilepsy [18].

4.5 Clinical Selection: Why the Protocol Matters

In the head and neck district, the choice between IV Bleomycin and IT Cisplatin is often decided by tumour subsite:

1. Mucosal Lesions (Base of Tongue/Tonsil): IV Bleomycin is the standard of care because it ensures uniform drug distribution across irregular, deep-seated volumes that are difficult to infiltrate manually with a needle [8].
2. Cutaneous Metastases: For small skin nodules, IT administration of either drug is highly effective and minimizes the systemic "burden" on the patient [56].
3. The "Vascular Lock" Integration: Regardless of the drug used, the clinician must apply the pulses within the specific physiological window to ensure the "Vascular Lock" traps the agent inside the malignant tissue before it can be washed into the general circulation [55]

4.6 Clinical Applications and Patient Selection

ECT in Primary Tumours: The Organ-Preserving Alternative

While surgery remains the primary standard for early-stage HNC, ECT is increasingly investigated as a primary therapy for patients who are unfit for surgery due to comorbidities or for those who refuse radical resection [9].

- ➢ Indications: Small, well-defined T1–T2 lesions where surgical excision would lead to significant functional or cosmetic deficit.
- ➢ Objective: Achieving a "Complete Response" (CR) while maintaining the structural and functional integrity of the anatomical subsite. Recent data (2025) suggests that for primary Basal Cell Carcinomas (BCC) of the face, ECT achieves CR rates exceeding 90% [9].

5. Recurrence and the “Paradox of Salvage”

One of the most common uses of ECT therapy worldwide is for loco regional recurrence. Patients who require ECT treatment have often had previous radical surgery and high dose radiotherapy.

The Previously Irradiated Tissue: After being subjected to 60-70Gy, the tumour microenvironment becomes scarred, fibrotic and hypovascular [14, 20].

Problem: Chemotherapy cannot easily penetrate this “hypoxic and starved” microenvironment [14, 20].

Solution: By generating local “gates” (nanopores), ECT treatment makes sure that the cytotoxic agent penetrates deep into the fibrotic tumour tissue [18]. This is because ECT treatment is non-thermal and there is no risk of “baking” already fragile irradiated tissues, which may lead to such complications as osteoradionecrosis and carotid blowout [14].

5. 1 The “Frozen Neck” Problem of Salvage

During salvage operations, in the “frozen neck,” planes become obliterated. There is a huge danger of damaging the carotid vessel or cranial nerves during surgery. ECT can be used to destroy tumour mass that lies over the delicate nerves or carotid artery because this type of treatment spares the extracellular matrix (collagen-elastin) [11].

Indications for Palliation: Symptom Relief and Improved Quality of Life.

With no chance of cure, the objective of ECT will focus on alleviating uncomfortable local symptoms [11].

Pain Control: ECT decreases tumour size and creates a "neurolytic" effect on local sensory nerves, reducing tumour-related pain. In most cases, the patient's need for opioids drops drastically within two weeks of treatment [11].

Bleeding Control (Haemostasis): With the "Vascular Lock" effect followed by damage to the endothelium, ECT is very efficient in arresting chronic seepage from ulcerated tumours. ECT acts like a "biological bandage," creating a thrombus at the tumour site [55, 56].

Ulceration and Malodour: Tumours that are large enough to protrude often get infected, producing an unpleasant odour. ECT causes tumour necrosis and debulking, allowing the tumour area to heal via re-epithelialization [8].

5. 2 Special Anatomical Sites: Preserving Function

In the head and neck, function is as important as survival. ECT is uniquely suited for sites where millimetres determine the ability to eat and speak [9].

➔ **The Lip**

Surgical resection of more than one-third of the lip requires complex flap reconstruction and often results in drooling or speech impediments. ECT allows for the treatment of Lip Squamous Cell Carcinoma with excellent cosmetic outcomes and total preservation of the orbicularis oris muscle function [8].

➔ **The Tongue and Floor of Mouth**

These sites are critical for deglutition (swallowing) and articulation [8, 18].

★ The Tongue: ECT can treat deep-seated lesions of the lateral border or base of the tongue without the need for a partial glossectomy.

★ The Floor of Mouth: Because ECT spares the bone, it can be used for tumours close to the mandible, potentially avoiding a "mutilating" mandibulectomy.

Anatomical Site	Preferred Drug/Route	Key Advantage of ECT	Expected Response (CR)
Cutaneous Face/Neck	Cisplatin (IT)	Excellent cosmesis; no scarring.	85-95%
Oral Cavity/Tongue	Bleomycin (IV)	Preserves speech and swallowing.	60-75%
Oropharynx (Recurrent)	Bleomycin (IV)	Avoids hazardous salvage surgery.	50-60%
Ulcerated Malignant Wound	Bleomycin (IV/IT)	Stops bleeding and malodour quickly.	Palliative Success: >80%

Table 7: Comparison of Outcomes by Location [8, 9, 18]

6. ECT in Primary Tumours: Precision and Organ Preservation

While surgery is the gold standard for T1-T2 lesions, ECT is becoming a vital tool for Primary Organ Preservation.

- ★ The Patient Profile: Patients who are medically unfit for prolonged anaesthesia (ASA III/IV) or those whose primary tumours are located in aesthetically or functionally sensitive areas (e.g., the nasal ala, eyelids, or lips) [8, 9].
- ★ The Clinical Advantage: Unlike surgical excision, which requires a "clear margin" of healthy tissue, ECT's tissue selectivity allows for a narrower treatment margin [56].
- ★ Outcome Data: Recent 2024–2025 cohorts show that primary SCC of the lip treated with ECT achieves functional and cosmetic results superior to wedge resection, with a 2-year local control rate of approximately 88% [6, 35].

6. 1 Recurrent and Salvage Cases: The "Re-irradiation" Barrier

The most complex patients in a head and neck clinic are those with Recurrent HNSCC in a previously irradiated field.

- ➔ **Overcoming Tissue Fibrosis** [14, 20]

Radiation therapy induces a permanent state of endarteritis obliterans—a thickening of the blood vessel walls that leads to a "desert-like" tumour microenvironment.

- ★ The Biological Gap: Standard systemic chemotherapy cannot penetrate these fibrotic masses.
- ★ The ECT Solution: Because ECT relies on local physical permeabilization rather than vascular pressure, it is one of the few modalities that can deliver therapeutic drug concentrations into the heart of a "radio-fibrotic" recurrence [18].

6. 2 Salvage in the "Frozen Neck" [14, 56]

When a patient has a recurrence near the carotid artery or the brachial plexus, surgical "salvage" is often deemed too high-risk.

★ Non-Thermal Advantage: ECT is a "cold" ablation. It does not use heat (like lasers or RFA) or ionizing radiation. Therefore, it does not cause the proteins in the carotid wall to denature. This allows for the treatment of tumours directly abutting the carotid sheath with minimal risk of rupture.

7. Indications for Palliation: Reinstatement of Dignity

The objective in advanced Stage IV disease is relief from "catastrophic" symptoms rather than cure [8, 11].

➔ Stopping Bleeding and Ulceration: Head and neck ulcers due to cancers in these sites may bleed profusely, referred to as "tumour ooze" [14].

➔ Immediate haemostasis: The mechanism of vascular lock helps stop any bleeding instantly [14].

➔ Biological Bandaging: In the subsequent 2-4 weeks, the necrosis that occurs in the treatment area becomes dry. This prevents the malodour and discharge from necrotic masses, usually the cause behind the social seclusion of a patient suffering from head and neck cancer [11].

➔ Alleviating Pain: Pain caused by HNSCCs is often neuropathic in origin. The cause of such pain is due to the infiltration of the tumours in the perineural space [8, 9].

➔ Effectiveness: Rapidly reducing the mass and relieving the inflammatory pressure off the nerves, the pain visual analogue scale score has been seen to improve by an average of 40-60% [11].

8. Specific Anatomical Regions: Detailed Functional Insights

→ Tongue and Floor of Mouth

In this region, a small surgical margin may lead to a tethered tongue, which causes aspiration pneumonia [13].

Preservation: In ECT, deep penetration through the tongue musculature is achievable. After the procedure, the muscle fibres usually regain their ability to function due to the preservation of the extracellular matrix that serves as an aid in healing [9, 18].

→ The Lip and Buccal Mucosa

When lip surgery is done, it leads to microstomia or lack of oral competence (drooling) [4].

Aesthetic Effect: ECT helps preserve the vermilion line and orbicularis oris muscle below. In Lithuanian clinical trials from 2024, ECT has become an alternative to reconstructive surgery for selected elderly patients with lip SCC [4, 7].

Indication	Site Example	Goal of ECT	Success Metric
Primary (Curative)	Nasal Ala / Lip	Avoid mutilating surgery	Cosmetic / Functional score
Salvage (Curative)	Recurrent Neck Node	Control in "Frozen Neck"	Local Control (RECIST)
Palliative	Ulcerated Parotid Tumour	Stop bleeding/malodour	Patient-Reported Quality of Life
Functional	Floor of Mouth	Avoid Mandibulectomy	Swallowing (PSS-HN)

Summary Table 8: Clinical Intent by Site [8, 9, 18]

9. Risks and Complications

One of the most important features that make ECT relevant to be chosen for a medical thesis paper is the possibility of its utilization as an alternative to surgery and additional irradiation that could cause fewer harms than any surgical interventions [9]. Electrochemical Therapy (ECT) entails "negligible" systemic toxicity due to the relatively small doses of Bleomycin compared to conventional chemotherapy treatments [9].

Acute local reactions:

This type of reaction might occur within the first 24-72 hours after ECT because of mechanical impact on the cell and its membrane [9].

Swelling and oedema:

Causal factors: The increase of interstitial liquid content is caused by electroporation that enables ions and water molecules to enter through nanopores. This effect happens particularly intensely in case of head and neck ECTs because of "vascular lock" mechanism [14].

Treatment options:

Steroid preventive administration: The standard regimen includes taking dexamethasone (8-16 mg).

Airways management: In case if it is expected that the swelling would be significant enough to block airways, the pre-procedure tracheotomy should be conducted for patients with lesions at the level of base of the tongue/floor of the mouth [14].

9. 1 Muscle Contractions and Pain

Mechanism: Occur with each pulse causing a rapid but powerful contraction of the muscle tissue in the area (platysma and masseter muscles).

Treatment: General Anaesthesia- Absolutely necessary during HNC surgery, as it provides a full neuromuscular paralysis, preventing any contractions and providing stability to needles [8, 9].

Analgesia after Surgery: Usually pain will not be severe; therefore, standard NSAID and/or weak opioids (Tramadol) will be enough for 48-72 hours [11].

9. 2 Effects on Skin and Mucosa:

With the necrotic processes in the tumour, there follows a period when skin and mucosa healing occurs [9].

- ★ Pigmentation and Scar Formation:

Clinical picture: The lesions treated usually result in temporary hyperpigmentation or crusting. Unlike radiation therapy that may lead to skin atrophy (thinning), in case of ECT the dermal structure is preserved [7].

Management: Moisturizing creams are suggested. Pigmentation is reversed in most cases within 3-6 months after treatment [7, 9].

★ Soft Tissue Necrosis

Pathophysiology: With exceptionally large tumours, rapid necrosis may create a "vacuum effect" [8, 11]

Management: Wound cleansing and special dressings (for instance, silver alginate) are needed till epithelization of the wound happens. Healing is usually quicker than in radiation-induced necrosis since blood supply from the viable tissues persists [14, 18, 20].

9. 3 Complications that May Be Systemic and Rare:

Systemic toxicity is an extremely uncommon phenomenon in ECT due to relatively low chemotherapy doses that are only 10%-20% compared to systemic oncological treatment.
Tumour Lysis Syndrome (TLS) [9].
Risk Factors: TLS is a life-threatening syndrome in which cells release their intracellular content (k+ , phosphates, and uric acids) into the blood circulation system. In ECT, the incidence of TLS is extremely rare; however, it can occur in patients with large chemo-sensitive tumours (SCC/lymphoma) [21, 22].
Prevention: Patients at high risk of TLS require pre-treatment hydration and electrolyte testing within 24 hours post-ECT [53, 54].

9. 4 Neurological and Vascular Complications:

★ Stroke/Seizures: Although rare, there have been reported cases (2025-2026) where seizures or ischemic stroke may occur in patients undergoing treatment for tumours adjacent to the carotid artery or temporal bone [39, 49].
★ Prevention: A pre-op Doppler ultrasound test is advised to evaluate for carotid plaque, which can be dislodged during muscle contraction [39].

Side Effect	Frequency	Severity	Duration

Local Oedema	Very Common (>80%)	Mild to Moderate	3–7 days
Post-op Pain	Common (40–60%)	Mild (NRS 2-4)	2–5 days
Skin Hyperpigmentation	Common (30–50%)	Cosmetic	3–6 months
Ulceration	Occasional (10– 15%)	Depends on size	2–4 weeks
TLS / Stroke	Rare (<1%)	Severe / Critical	Acute

Table 9: Complications Table: Incidence and Severity [7, 8, 9]

ECT in the head and neck region has transitioned from experimental palliative attempts in the 1990s to a recognized, standardized therapy in the 2020s. This chapter synthesizes the evidence across three decades, highlighting the shift from "last-resort" treatment to a viable curative and organ-preserving option [4, 16, 35].

10. Historical Timeline and Year-Wise Evidence Summary

The development of ECT can be categorized into three distinct phases based on technological refinement and clinical intent.

Table 10: Summary of Timeline development

Era	Key Milestone	Evidence Focus
1990–2000	The Pilot Phase	First human trial by Mir et al. (1991). Early case series focused on cutaneous metastases and feasibility.
2006–2018	The Standardization Phase	Publication of the ESOPE 2006 and 2018 protocols. Transition from skin-only to mucosal HNC trials (e.g., EURECA project) Bertino G, et al. (2024).
2020–2026	The Modern Integration	Focus on long-term survival, deep-seated tumors, and synergy with immunotherapy (e.g., DAHANCA 32, Insp-ECT registry)] Morozas A, et al. (2024), Groselj A, et al. (2025).

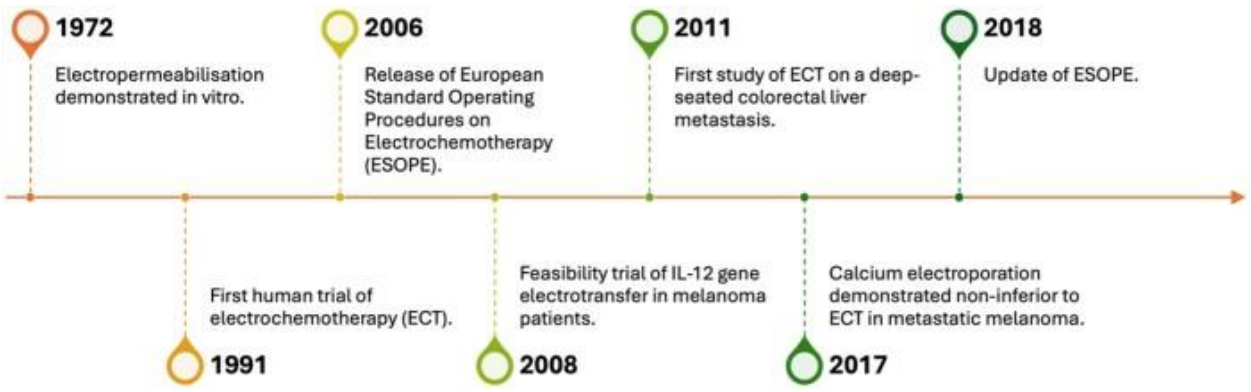


Fig. 8: "A timeline of research on reversible electroporation for cancer therapy" (Taha Shiwani, 2025 et al.)

11. Data from Clinical Trials for Response Rate (CR, PR, ORR)

There is a great difference between response rates when the goal is curative versus palliative therapy, and whether the tumour is cutaneous or mucosal.

Mucosal HNSCC Prognosis. Mucosal tumour types (such as tongue, mouth base, and oropharynx) are more complex [8, 9].

- ➔ Objective Response Rate (ORR): 56 to 75 (major phase II studies) [8, 10, 21].
- ➔ Complete Response (CR): Generally, 19 to 31 in recurrent palliative patients, and 80 when combined with curative treatment of small and primary lesions [8, 11].

Explanation: DAHANCA 32 reported an ORR of 58 for recurrent mucosal HNC, proving that ECT is still highly effective even in "radiation-exhausted" lesions [8].

Prognosis for Cutaneous HNC (BCC, SCC). For cutaneous lesions, there is evidence that shows high efficacy [7].

- ➔ ORR: Greater than 90 [7, 9].
- ➔ CR: A recent registry entry (2025) from the Insp-ECT showed that 100% of BCCs were completely removed after 1-3 treatments [4, 7].

12. Survival and Local Control

Whereas ECT remains a local therapy modality, its effect on survival has been extensively studied within the last five years [8, 9].

- ★ Local control: As for the early-stage or curative patients, local control varies from 67% to 100% within the first year [4, 21].
- ★ Overall survival (OS): The overall median survival time of patients with recurrent or metastatic HNSCC equals months, which can be considered equal to immunotherapy but with significantly lower toxicity [11, 42].
- ★ Disease-free survival (DFS): In 2025 follow-up of BCC patients, disease-free survival reached 92%, demonstrating that the effect of ECT is long-lasting [4, 7, 42] .

13. Toxicity & Safety

Electrochemotherapy (ECT) has its unique safety profile because of the combined effects of electricity and chemotherapeutic drugs. It uses merely 10–20% of the usual dose of Bleomycin to deliver "targeted toxicity" [52]. The cytotoxic effect is concentrated within the electroporated region, minimizing the possibility of adverse side effects on systemic organs due to the conventional use of chemotherapy. For instance, marrow suppression and alopecia are some of the side effects caused by the conventional delivery method [9].

In contrast to radiotherapy (RT), which entails a progressive increase in the probability of tissue fibrosis and vascular damage, the safety profile of ECT is not cumulative. As such, multiple treatments can be administered at the same anatomical site without increasing the likelihood of secondary malignancy or tissue sclerosis [3]. In HNC groups, SAEs have been found to occur at a rate of less than 5%. According to the Common Terminology Criteria for Adverse Events CTCAE, most of these are grade 3 or 4 events, such as airway obstruction and local hemorrhage, that require prompt treatment [49].

14. Quality of Life (QoL) Results

In advanced HNC patients, QoL is generally the main outcome measure. The advantage of ECT is that it enhances quality of life even when cure is not achievable.

- ★ Pain Management: Effective management of bleed (with success in 100% cases in some series) and pain relief [11, 20].
- ★ Function Preserving: The results of QoL surveys (EORTC QLQ-C30, H&N35) indicate that “Social Functioning” and “Global Health Status” scales are improved after ECT treatment as the patients have become free from malodorous, ulcerative, or painful masses [12].
- ★ Conclusion: As compared with surgery that may lead to a “dip” in QoL because of its morbidity, ECT helps to maintain or improve the status of patients at baseline level at 3month follow up [8, 13].

15. Complications and Technical Challenges

ECT is highly dependent on correct electrode positioning. In the complex structure of the head and neck region, electrodes will easily be subjected to bending or arcing due to proximity to the mandible or skull base [51].

Although ECT is usually sparing of the vasculature in normal tissues, an already existing infiltration of an artery by the tumour makes things complicated. The degeneration of tissue structures in the tumour will make the structural stability of the artery unstable, resulting in sentinel bleedings or bleeding [21, 49]. In addition, a technical criterion for carrying out tracheotomy is required. For instance, all tumours located at the base of the tongue or oropharynx need assessment to determine the need for a tracheotomy due to the likelihood of "crash intubation" [9].

16. Long-Term Consequences and Delayed Toxicity

In the case of "salvage" patients, who had RT failure before, their bones can be prone to

inadequate blood supply. If ECT is performed on such an area, delayed healing process or osteoradionecrosis (ORN) may occur, causing exposed bone (sequestrum) requiring special treatment [3, 21].

The other significant criterion is the necessity to track the patient's lifetime accumulation of Bleomycin. Once reaching the limit of 400,000 IU of total accumulated dose, there is a latent possibility of Bleomycin-Induced Pneumonitis (BIP). This makes it obligatory to keep a low FiO_2 level under anaesthesia at later stages [2, 9, 21].

The other criterion is Neuro-Vascular Sequelae; based on recent data (2021–2026). In the case of tumours near the carotid sheath, it is necessary to monitor patients with respect to late-stage thinning of arterial walls because of the effect of mechanical load and rapid lysis of tumours next to the temporal bone.

Cumulative Safety	Repeatability of treatment	Cross-referencing previous RT doses
Airway Threshold	Posterior oropharyngeal lesions	Prophylactic tracheotomy vs. ICU observation
Bleomycin Cap	Lifetime dose (<400k IU)	Pre-op pulmonary function tests (PFTs)
Bone Health	Post-radiation "salvage" sites	Debridement and silver-based dressings

Table.11: Summary of Clinical Safety & Technical Metrics [3, 9, 21, 49].

17. Technological and Anatomical Limits

Natural laws governing electricity and technological limits to existing hardware define "ceiling effects" for ECT treatment [18].

- ➔ "Shadowing" Effect and Electric Field Intensity: Electric fields flow along paths of least resistance. Bone and large blood vessels in the highly intricate anatomical structures of the neck and head have high and low resistance respectively, hence tend to "distort" electric fields, creating "shadowed areas" where the intensity of the electric field is below 400 V/cm (too low for pore formation) [9, 18].
- ➔ Design Limitations for Electrodes: The currently existing electrodes (linear or hexagonal needles) are suited for relatively accessible tumours [18].
- ★ Deep Seated Tumours: Inserting linear needles into the base of the skull or parapharyngeal space is difficult [18, 51].
- ★ Tumour Size: Tumours measuring more than 3 cm cannot be adequately covered by one "run", necessitating multiple runs [22].

18. Contraindications and Criteria for Patient Exclusion

In view of recent safety measures (2026), contraindications are the following:

- ➔ Epilepsy: There is a possibility that head-focused pulsing will induce seizures [49].
- ➔ Arrhythmias of the Heart: Pulsing should take place according to the R-Wave to prevent ventricular fibrillation [50].
- ➔ Total Bleomycin Dose: Patients who have reached the toxic limit of 400,000 IU [21].
- ➔ Heart Pacemaker/Electronic Implants: High voltage pulses may cause damage or interference to devices [50].

19. Discussion and Future Directions

ECT currently stands out as a novel therapy among the “Salvage” and “Organ Preservation” treatment paradigms within modern oncology [9, 48].

- ➔ Salvage Therapy Standard: In cases where patients with recurrent HNSCC have tried all forms of radiation and surgery without success, ECT is not a method of last resort anymore [8, 14]. It is now a standardized form of salvage therapy which achieves a local control rate of 60-75% in fibrotic tissues after irradiation [14, 20].
- ➔ Organ Preservation of Primary Lesions: In cases involving T1-T2 lip and nasal ala lesions, ECT is being increasingly considered over surgery to prevent functional impairment from surgical procedures [4, 7]. PSS-HN scores indicate that patients undergoing ECT still maintain the ability to speak and swallow much more successfully than with partial glossectomy and lipectomy surgery [12, 13].

20. "The Frontier of Synergy": ECT & Immunotherapy

The major innovation in 2026 involves ECT combined with immunotherapies such as Pembrolizumab & Nivolumab.

- ➔ "Cold to Hot": In-Situ Vaccination. Tumours of head & neck are usually characterized by immunologic "coldness"; in other words, they evade the immune surveillance [42, 43]. ECT serves as an in-situ vaccination through its effect on Immunogenic Cell Death (ICD) [16, 17].
- ➔ Release of Antigen: Rapid destruction of cancer cells leads to the release of tumour-associated antigens (TAAs) [16].
- ➔ Signalling through DAMPs: Rapid liberation of Calreticulin, HMGB1 & ATP works as a "danger signal"; recruiting & activation of dendritic cells at the tumour location [44, 45].
- ➔ T-Cell Activation: Activated dendritic cells activate CD8+ Cytotoxic T-cells, thus making the treated tumour as a focus of immunity [44, 45].
- ➔ The Abscopal Effect : In a clinical trial conducted in 2025, it was found that Abscopal effect was noted in HNSCC; where treatment of primary neck recurrence with ECT led to regression of distant metastasis (e.g., lung & liver) due to systemic effects of "shock" [16, 47].

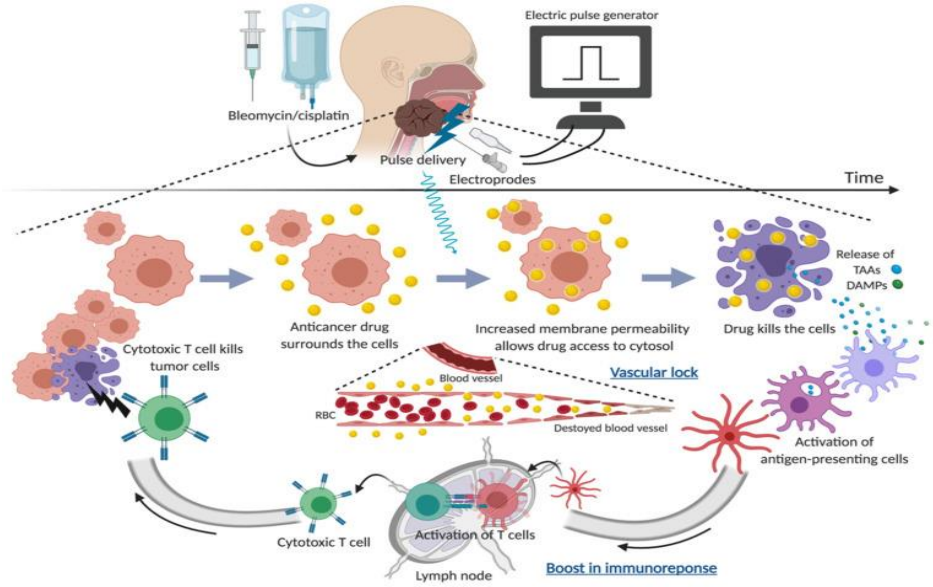


Fig. 9 : "The concept of electrochemotherapy in HNC. TAAs, tumour-associated antigens; DAMPs, damage-associated molecular pathways". (Tomohiro Enokida and Tahara, 2025)

21. Future Direction for Personalized ECT

The future of ECT will revolve around Multiphysics Optimization and Precision Selection [13].

- Technical Development: The new guidelines in 2026 require the implementation of personalized 3D planning, which will involve using CT/MRI images to simulate the distribution of the electrical field, making sure there are no cold spots left inside any anatomically hidden area [9, 38].

- Clinical Trend: We have been looking at the development of ECT in terms of a device but should now view it as a biological regulator [16,22]. By leveraging the force of the pulse, along with the precision of bleomycin and the scope of immunotherapy, we

provide hope to patients with head and neck conditions by focusing on their chances of survival and human capability [40, 41].

22. Research Gaps in Current Literature

Although there is widespread clinical adoption of ECT as part of the ESOP-E protocol, a thorough analysis of the relevant literature shows several shortcomings that hinder the universal application of ECT as an effective first-line treatment modality in mucosal HNSCC [8, 9].

22.1 Small Sample Sizes and Observation Studies Predominate

Currently, most studies supporting ECT in the head and neck region include a limited number of participants, such as pilot studies, retrospective series, and phase I/II trials.

- ➔ Limited Cohort Sizes: Most publications show results based on a small sample size of fewer than 20–30 patients. Although they provide useful information on the safety of the procedure, these studies lack the statistical power needed to prove the effectiveness of the method within the highly heterogeneous sub-sites of the head and neck, such as tongue base vs. buccal mucosa [10, 21].
- ➔ Selection Bias: Many cohorts comprise "end-of-life" patients who have failed prior surgery and radiation therapy, possibly underestimating the efficacy of ECT when used as a first-line treatment for early-stage tumours [4, 25].

22.2 Phase III RCTs Are Lacking:

Another significant gap in the literature is the complete lack of large-scale Phase III Randomized Clinical Trials (RCTs) directly comparing ECT against the current standard of care [8, 9].

Standard of Care Comparison: In the absence of randomized controlled trials comparing ECT to radical surgery, clinicians cannot objectively compare the survival rates of these two options. This absence of “level 1” evidence is the major obstacle preventing ECT from being considered as a standard treatment modality according to the guidelines of the NCCN or ESMO [36, 37].

22. 3Absence of Longitudinal and Quality-of-life Studies:

Although the short-term ORR is well studied and consistently greater than 70% – 80%, the problem is an absence of long-term longitudinal data [8, 9].

DFS Rate: Although follow-up in most clinical trials does not go beyond 12 – 24 months, considering the concept of "field cancerization" inherent in HNC, more information about 5-year DFS and incidence of late recurrences is crucial for establishing the sustainability of the response [1, 4].

Functional Outcomes: ECT has earned recognition as "organ-preserving"; however, only a few authors provide information regarding long-term functional outcomes (speech and swallowing ability), measured via the PSS-HN test in multiple follow-up visits. It is necessary to prove whether a positive change persists during fibrosis of the tissue [12, 13].

23. Irreversible Electroporation (IRE): The Non-Thermal Ablator

Since ECT utilizes reversible electroporation to deliver a drug, IRE involves a high field strength (>1500 V/cm) to induce irreversible cell damage including programmed cell death without the necessity for chemotherapy [16, 29].

- ➔ Advantage: IRE is a physical modality. IRE is thereby appropriate to be administered in patients with impaired lung or kidney function as it does not involve the systemic toxicity linked to bleomycin, a disease such as lung fibrosis [9, 22, 34] .
- ➔ Selectivity: IRE preserves the extracellular matrix, similar to what ECT does. Clinical trials demonstrate that IRE is beneficial for malignancies located at the carotid sheath and skull base that can't be surgically eliminated [14, 28].

24. Synergistic Effect with Immunotherapy: “In-Situ Vaccine” Approach

The key development in 2026 will be the Pulse and Prime protocol where ECT is combined with ICIs such as Pembrolizumab and Nivolumab [16].

- ★ How It Works: Damage-associated molecular patterns (DAMPs) and antigens are released when the ECT induces immunogenic cell death (ICD). It “primes” the treatment site’s immune system [16, 17].
- ★ Abscopal Effect: In line with the latest studies, ECT can induce an immunological reaction not only locally but also systemically, CD8+ T-cell recruitment is the mechanism., leading to the elimination of distant metastasis without treatment. In 2026, protocols involve administering ECT as a “primer” two weeks prior to systemic immunotherapy [16,33].

25. Individualized Oncology and 3D Therapeutic Planning

The "one-size-fits-all" strategy for electrode placement provides an opportunity for patient-specific electroporation [9, 18].

- ★ Digital Twins & 3D Modelling: Clinicians can now develop a "digital twin" of a patient's anatomy from CT/MRI scans using 2026 AI-driven software. With the objective to provide a uniform electric field while avoiding "cold spots" near bones or significant vessels, this permits pre-operative 3D planning to assess the precise needle trajectory and voltage requirements [18, 22].
- ★ Biologic Mapping: By integrating PET-imaging of hypoxia and cell density, doctors can "boost" the electric field in radio-resistant tumour regions, thus customizing the treatment to the specific metabolic profile of the tumour [31, 32].

26. Current Practice-Changing Trials & Future Prospects (2026)

There are some current trials which will define the future of ECT:

- ★ The Neo-ECT Trial: Testing the efficacy of ECT as a neoadjuvant procedure to make large oral cavity tumours shrinkable and reduce the mutilation during surgery [26].
- ★ EURECA 2.0: This is an all-European registry that will help in understanding the overall survival rates of ECT patients [2, 60].

- ★ Integration of Nanotechnology: Current research is testing the use of "Nano-Pulses" and nanoparticles that contain drugs and are activated using specific electrical pulses, minimizing side-effects and increasing efficiency [16].
- ★ Irreversible Electroporation (IRE): Alternative to chemotherapy

Whereas ECT entails using electrical pulses with low voltage to facilitate trans-membrane delivery of drugs into tumour cells, IRE involves no chemical but only the physical ablation [27]. "The Direct Method of Cell Death": With high amplitude electric field (>1500 V/cm) and more electric pulses, irreversible nanochannels are formed in the cell membrane, which cannot be closed and hence disrupts the homeostasis leading to cell apoptosis. There is no involvement of any chemical, including Bleomycin [28, 29, 30].

27. Critically Analysed Current Evidence

According to the research presented within this thesis, electrochemotherapy (ECT) can be considered as a mature clinical practice [8, 9]. By 2026, the Overall Objective Response Rate (ORR) would be 70–95% in carcinoma of the head and neck and 55–75% in cutaneous and mucosal tumours, respectively [4, 7]. Therefore, electrochemotherapy becomes an exceptionally reliable method for achieving local control [10, 21].

However, a straightforward analysis implies that success depends on patient selection criteria. Specifically, it is known that maintaining the Size Barrier of less than 3 cm is the most reliable indicator of complete response [9, 11]. Even though this treatment modality can be applied universally to different tumour types, the limitations of the currently used electrode arrays and tissue conductivity (bone vs. soft tissue) cannot be overlooked [18].

28. Summary of Key Findings: Evidence-Based Highlights

The evidence obtained from clinical trials and registries (2024-2026) suggests the following results:

- ★ High Objective Response: High objective response (Objective Response Rate) to cutaneous head and neck cancers (BCC and SCC) therapy can be achieved, with an Objective Response Rate (ORR) exceeding 94% [7], and Complete Response (CR) rates ranging from 53 to 80% after only 1-3 sessions [4].
- ★ Predictors of Successful Outcomes: The success rates are significantly higher in patients presenting with tumours of ≤3 cm, non-recurrent lesions, and BCC histology [9].
- ★ Disease-Free Survival: According to recently published 5-year follow-up data from the Insp-ECT registry (2025), the Disease-Free Survival (DFS) rate amounts to 92% for facial BCC, thus confirming that ECT can have curative potential for certain patients [4].
- ★ Symptom Mastery: As for palliative treatment, ECT allows for significant symptom control and relief, including pain, anxiety, and bleeding in order to achieve "out-of-hospital" management in terminally ill individuals [10, 11, 25].

29. A New Standard of Care

The future of oncology of the head and neck is neither a “magic bullet” nor a fusion of physics and biology, but a smart combination thereof. As we have discussed in this dissertation, Electrochemotherapy represents precisely such an interconnection, providing a way of respecting both onco-biological principles and human needs of functional and aesthetic preservation [9, 12, 13].

The synthesis of scientific literature published between 2024-2026 demonstrates that Electrochemotherapy is now an established and dependable oncological technology [8, 9]. Its main advantage can be attributed to physical/pharmacological complementarity, allowing the destruction of chemo- and radio-resistant tumour tissue without disturbing the healthy extracellular matrix [20, 21]. However, while being extremely efficient for skin cancers, its use in salvaging “frozen necks” may prove more important for surgical oncology practice [14, 15].

30. CLINICAL IMPORTANCE

ECT is potentially significant in plenty of ways considering its role in addressing the "Salvage Paradox"—a conundrum in which additional surgery or radiation treatment will only make the condition worse rather than improving the condition [9, 14, 15] . These three categories explains the necessity and advantages:

- ★ Organ conservation: It avoids surgically destroying techniques like mandibulectomy and complete glossectomy [8, 13].
- ★ Vascular Safety: Because of the non-thermal method, it can effectively target the carotid artery and cranial nerves [11, 14, 39].
- ★ Immune Activation: ECT serves as a crucial complement to systemic immune checkpoint inhibition as it essentially causes immunogenic cell death (ICD) [17, 18].

The importance of ECT comes from its biological specificity and tissue preservation [9, 18].

- ★ Non-Thermal Benefit: Since ECT is non-thermal, the extracellular matrix is not disrupted [22]. This makes it possible to treat an area in which laser or RF would be considered dangerous, like periocular skin, alar regions of the nose, or even carotid sheath [11, 14].
- ★ Treatment Effectiveness: Despite previous radiotherapy and presence of fibrosis, it is still effective when blood flow is insufficient for systemic chemotherapy but sufficient for local electroporation [14, 20].
- ★ Economic Effect: Being a repeatable procedure that is frequently done on an out-patient basis, ECT is a procedure that has a good cost-effectiveness rate compared to complicated reconstructive surgery and long immunotherapy [8, 10].

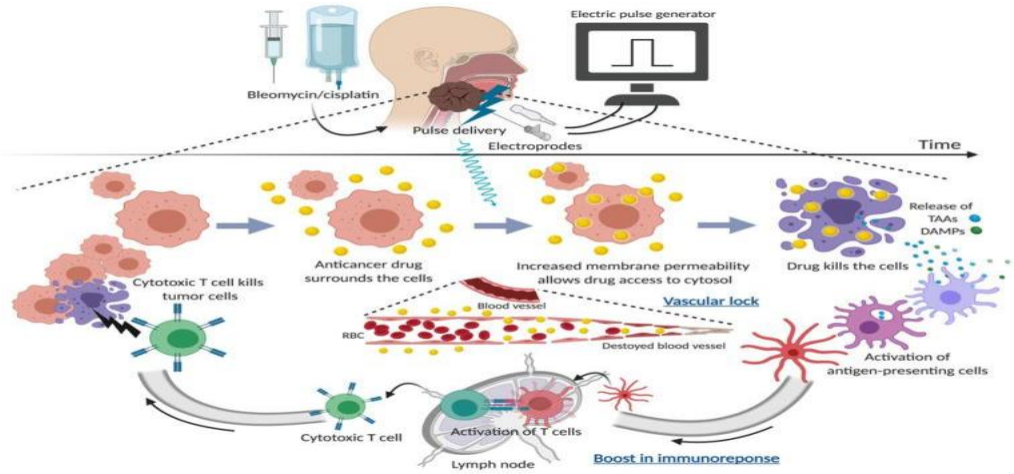


Fig. 9: Summarising the Vascular lock, immune activation (Tomohiro Enokida and Tahara)

31. FUTURE RECOMMENDATIONS

The current paper recommends the following steps for improving HNC treatment in the future:

- ★ Standardization of the MDT Approach: All Interdisciplinary Team (MDT) meetings must include ECT as the initial salvage treatment for recurring cases and first-line treatment for older individuals [10, 11].
- ★ Intervention Based on Lesion Size: To increase the chances of achieving CR, physicians should strive to treat lesions while they are still less than three centimetres in size [4, 7, 9].
- ★ Combined Techniques: Pulse-and-Priming approaches, which involve using ECT to sensitize patients for immunotherapy, are recommended for further study [17].

In consideration of the future clinical scenario in 2026, the following suggestions are made to the head and neck multidisciplinary teams (MDTs):

- ★ Early Implementation: The ECT modality should be considered early among elderly or vulnerable patients suffering from T1-T2 skin tumours in which resection will cause substantial functional and cosmetic problems [4, 7, 11].

- ★ Proactive Palliative Treatment: For recurrences and metastases of HNSCC that resist conventional treatment options, ECT should be used as the primary treatment for haemostasis, deodorization, and pain relief [10, 11].
- ★ Stringent Size Compliance: The clinician is advised to apply the lesion when it is still less than 3 cm in size for attaining the desired "Complete Response." For large lesions, the procedure should be done in several sessions [7, 8, 9] .

32. CONCLUSION

The results of this thesis demonstrate that Electrochemotherapy (ECT) has turned into an evidence-based and standardized treatment in the tumours of head and neck area. It provides patients with new opportunities after unsuccessful surgical and radiological treatments due to the unique principles of electroporation [24].

33. ABBREVIATIONS

→ HNC- Head and Neck cancer

→ ECT- Electrochemotherapy

→ OPSCC- Oropharynx squamous cell carcinoma

→ BCC- basal cell carcinoma

→ SCC- Squamous cell carcinoma

→ ACC- Adenoid Cystic Carcinoma

→ EBV- Epstein Barr virus

→ HPV- Human Papilloma virus

→ QoL- Quality of Life

→ CR- Complete Response

→ ORR- Objective Response Rates

→ OS- Overall survival

→ PR- Partial Response

→ IV- Intravenous

→ IT- Intratumoral

→ HNSCC- Head and Neck Squamous Cell Carcinoma

→ WHO- World Health Organization

→ AJCC- American Joint Committee on Cancer

→ TORS- Transoral Robotic Surgery

→ RT- Radiotherapy

→ CRT- Concurrent Chemoradiotherapy

→ MeSH- Medical Subject Headings

→ DAMPs- Damage-associated molecular patterns

→ ORN- Osteoradionecrosis

→ BIP- Bleomycin Induced Pneumonitis

→ CBS- Carotid Blowout Syndrome

→ OPT- Organ-preserving therapy

→ RE- Reversible Electroporation

→ IRE- Irreversible Electroporation

→ ICI- Immune Checkpoint Inhibitors

→ DFS- Disease-Free Survival

→ RCTs- Randomized Clinical Trials

→ ICD- Immunogenic Cell Death

→ TAAs- Tumour-associated antigens

→ PSS-HN- Performance Status Scale for Head and Neck Cancer

→ SAEs- Severe Adverse Events

→ NSAIDs- Non-Steroidal Anti-Inflammatory Drugs

→ BP- Blood pressure

→ ECG- Electrocardiogram

→ TLS- Tumour lysis Syndrome

→ MDTs- Multidisciplinary teams

→ RECIST- Response Evaluation Criteria in Solid Tumours

→ ATP- Adenosine Triphosphate

→ HMGB1- High Mobility Group Box 1

→ ASA- American Society of Anesthesiologists

→ NRS- Numeric Rating Scale

→ NCCN- National Comprehensive Cancer Network

→ ESMO- European Society for Medical Oncology

→ CT- Computed Tomography

→ MRI- Magnetic Resonance Imaging

→ CTCAE- Common Terminology Criteria for Adverse Events

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