Journal of Anatolian Wildlife Sciences
Journal Home-Page: https://dergipark.org.tr/en/pub/jaws
E-ISSN: 3108-673X

JAWS
x (x): x-x, 2026
DOI: xxxxxxx/jaws.2026.1480131

Review Article

Electrochemotherapy as an Emerging Alternative Treatment Option in Neoplasms of Pet Birds

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Abstract

The management of neoplasms in pet birds holds a significant place in veterinary oncology. Species within the Psittaciformes order are the most commonly diagnosed group and budgerigars are the most frequently affected species. Traditional treatment options for avian neoplasms are often limited and carry potential risks. As the demand for effective and less invasive therapies increases, electrochemotherapy has emerged as a promising alternative in veterinary oncology. The primary objective of this review is to investigate and assess how effective electrochemotherapy can be as a treatment method for neoplasms in pet birds, with a particular focus on Psittaciformes species. Additionally, emphasis is placed on the need to develop standardized protocols to fully confirm the efficacy of electrochemotherapy and achieve the best outcomes in avian oncology.

Keywords: Avian, Electrochemotherapy, Electropermeabilization, Electroporation, Neoplasia

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How to cite this article?

Ertürk EH, Özsoy S: Electrochemotherapy as an Emerging Alternative Treatment Option in Neoplasms of Pet Birds. JAWS, 2026 (Article in Press).
DOI: xxxxxxx/jaws.2026.1480131

Article ID: JAWS-2026-1480131
Received: 07.05.2024
Accepted: 17.11.2025
Published Online: 03.06.2026

INTRODUCTION

In recent years, significant advancements have been observed in the scientific understanding and methodological approaches to disease, care, nutrition, anesthesia, and analgesia in pet bird species. Alongside the increased lifespan of these species, there has been an increase in the prevalence of neoplastic diseases [1]. The increasing knowledge in the diagnosis and treatment approaches for neoplastic diseases in humans and domestic mammals has emphasized the need for more advanced diagnostic and treatment methods for neoplastic cases in pet birds [2].

Among pet birds, the Psittaciformes order represents the group with the highest incidence of neoplasia, accounting for approximately 3.6% of cases. Within this order, budgerigars *(Melopsittacus undulatus)* stand out as the most frequently affected species. On the other hand, the incidence of neoplasia in the Passeriformes order is much lower, at around 0.46%. The lack of case reports for specific orders or species may not accurately reflect the natural tumor resistance in cases where that order or species has not been widely studied or monitored. Histological examination of tissue samples from these animals may reveal higher incidence rates. The literature indicates an incidence of neoplasia in budgerigars ranging from 15% to 24% [3]. Cutaneous and subcutaneous lesions happen to comprise a significant place within all tumors in exotic birds [4]. In an investigation, skin tumors were reported to comprise of 57% of all tumors in budgerigars [5].

The establishment of a definitive diagnosis is crucial before determining therapeutic approaches and prognosis in neoplasms. Birds tend to camouflage their pathological conditions until the advanced stages as a result of their natural role as prey in their ecosystems [6]. Neoplastic conditions are typically diagnosed in the advanced stages of the disease. Clinical symptoms are often non-specific, and the progression of the disease is slow. This is particularly critical for internal organ neoplasms. Therefore, the possibility of neoplasia should

be considered in the differential diagnosis. In animals suspected of neoplasia, a detailed history should be taken, and particularly abdominal palpation should be performed [3]. External neoplasms can be identified through physical examination and the histopathological analysis of fine-needle aspiration or biopsy samples. The diagnosis of internal organ neoplasms is accomplished through radiography, ultrasonography, endoscopy, biopsy, or surgical interventions [7].

Due to the small body size of birds, the applicability of certain therapeutic approaches may be limited. The number of cases in the literature concerning avian oncology is limited, and the absence of epidemiological studies in this field restricts the veterinarian's capacity to provide a definitive prognosis and treatment outcomes to pet owners.

In neoplastic birds, the therapeutic approach should ideally target the eradication of the primary tumor. If this strategy is not feasible or results in failure, treatment can be directed towards options such as inhibiting tumor proliferation, mitigating symptomatic pain, preserving normal function, and correcting aesthetic deformities. The selection of therapeutic modules should be determined based on factors such as the histological classification of the tumor, anatomical localization, invasion and metastatic potential, pressure applied to adjacent anatomical structures, the patient's overall health, and the approach of pet owners towards treatment. Neoplasia management may involve the combined use of methods such as surgical resection or extirpation, radiotherapy, chemotherapy, and electrochemotherapy. The effectiveness of multimodal treatment approaches is significantly supported in the literature. The therapeutic protocol should be meticulously planned at the initial stage and should be comprehensively shared with pet owners, including potential costs, expected outcomes, potential complications, and the necessity of routine clinical check-ups. Tumoral response should be evaluated with short-term and long-term parameters throughout the treatment process, and these assessments should be conducted using quantitative methods whenever possible [3].

A biopsy is essential to determine the tumor's nature, involving cell collection through fine-needle aspiration or excision of part or all of the growth. Ideally, biopsies should sample both normal and abnormal tissue, as well as any inflamed or ulcerated areas. In cases of bone involvement, the biopsy should be taken from the lesion's center. An impression smear, in which a slide is pressed onto an ulcerated mass for cell collection, may also be used. These samples are then analyzed by a pathologist for definitive diagnosis [8].

Traditionally, surgical excision or limb amputation has been the primary method for treating neoplasia in birds. Many avian tumors respond well to surgery alone, with treatment failures often due to insufficient surgical margins or undetected metastasis, although metastasis in birds is relatively rare. The success of surgery depends on factors like the tumor's location, size, extent of involvement, biological behavior, and the bird's overall health. Tumors located on the skin are more likely to be cured through surgery alone compared to those involving deeper tissues or internal organs [3].

In surgical procedures, aseptic techniques are crucial, especially if adjunctive chemotherapy will be used, since many avian cancer patients may be older or immunocompromised. A "no touch" approach is recommended to avoid spreading cancer cells; for instance, excisional biopsies should be prioritized, and precautions such as early ligation of tumor blood supply, frequent changes of surgical gloves, and saline flushing of the site can be taken to minimize risks. When complete tumor excision is not feasible, debulking the mass can relieve symptoms like impaired movement, bleeding, and pain while potentially enhancing the bird's immune response and quality of life [3].

Inhalant anesthesia is typically the preferred method for both inducing and maintaining anesthesia in birds due to several key advantages. These include rapid induction and recovery times, ease of quickly adjusting anesthetic depth, and minimal metabolism required by the body. Additionally, inhalant anesthetics generally have minimal side effects on the cardiovascular and respiratory systems and low toxicity to organs, making them particularly suitable for birds with compromised liver or kidney function [9].

Electrochemotherapy is gaining increasing interest in exotic animal oncology as an emerging treatment option [10]. Electrochemotherapy combines the local or systemic application of chemotherapeutic agents with low membrane permeability, such as bleomycin or cisplatin, with electroporation directly applied to tumor tissue [11]. The purpose of this review is to assess the clinical and therapeutic outcomes of electrochemotherapy applications in neoplastic birds.

Electrochemotherapy

Electroporation or electropermeabilization is the process of temporarily increasing the permeability of the cell plasma membrane through specific electrical pulses. Via this procedure, molecules that the membrane would not normally allow or those with limited permeability can pass into the cytoplasm. Electrochemotherapy is an approach where electropermeabilization technology is combined with chemotherapeutic agents with the aim of facilitating the entry of antineoplastic drugs into the cell [2].

The electropermeabilization procedure aims to potentiate the cytotoxic effects of antineoplastic drugs. Particularly, the sensitivity of endothelial cells to the electropulsation of these drugs forms the biological basis for the vascular disruptive effect of electrochemotherapy [11].

The administration of chemotherapeutic agents is performed intravenously or intratumorally *(Fig. 1)*. In order to achieve an effective therapeutic response when electric pulses are applied to the tumor, it is essential for the drug to be readily available at a sufficient concentration. In this context, the timing between drug administration and the application of electric pulses is crucial [12].

In previous applications of electrochemotherapy (ECT) in birds, drug dosages have been administered intratumorally based on standard intravenous doses. Average doses range from 0.5 mg/kg to 2.5 mg/kg, adjusted according to the therapeutic response observed. During administration, these amounts are diluted with distilled water. Electrical pulses are typically delivered 2 to 5 minutes following drug administration.

Principle of Electrochemotherapy

The primary effect of the generated electric fields is to interact with the cell membrane, leading to an increase in membrane permeability [13]. When a cell is exposed to an electric field, a transmembrane potential arises due to the difference in electrical characteristics between the cell membrane and the cytoplasmic and extracellular environment. Reaching a specific threshold value of this potential triggers the formation of electropores in the cell membrane [12].

The formation of pores increases the membrane's permeability, allowing molecules that cannot typically pass through the membrane to enter the intracellular environment. Neoplastic cell membranes are less stable in structure compared to non-neoplastic cells. Under the influence of electrical pulses, the reorganization of the lipid bilayer, redirection of hydrophobic tails, and positioning of hydrophilic heads towards the newly formed pores occur. The pores formed in this process gain temporary stability through water bonds in the head spacing [13]. This reversible increase in permeability allows molecules, ions, and water to rapidly transfer between the two sides of the cell membrane [11]. The passage of molecules with a molecular weight of less than 4 kDa mostly occurs through a simple diffusion mechanism [12].

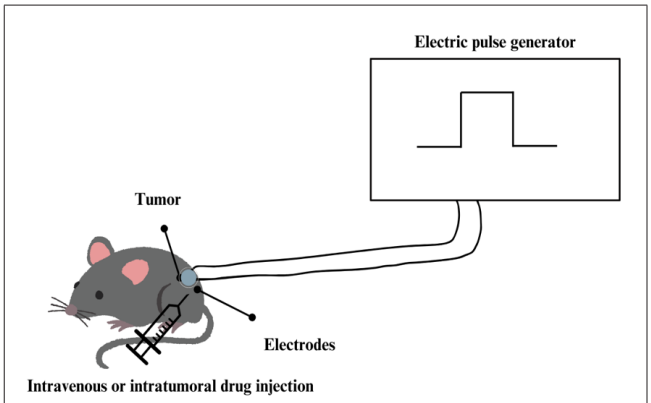

Fig 1. A schematic representation of the electrochemotherapy protocol applied to tumors. The drug is administered intravenously or injected directly into the tumor at doses that do not exhibit anti-tumor effects. After a certain interval that allows sufficient drug accumulation in the tumors, electrical pulses are applied to the tumor using plate, contact, or needle electrodes

When exposed to electrical pulses, a cell can exhibit two potential responses:

1- Returning the cell to its physiological balance, known as "reversible electroporation".

2- Undergoing necrotic changes, known as "irreversible electroporation" [11].

Reversible electroporation occurs when the cell membrane's permeability temporarily increases, and the cell regains its homeostatic balance. The characteristics of the electrical pulses are typically determined as square waveforms of eight pulses with amplitudes generally in the range of 100-1000 V and a duration of 100 milliseconds. Irreversible electroporation, on the other hand, is a mechanism where the magnitude and duration of the electrical pulses exceed the cells' adaptability, ultimately resulting in cell death. Typically, this phenomenon requires at least 80-100 pulses and amplitudes of up to 3000 V. Whether electroporation is reversible or irreversible is essentially determined by the intensity of the electric field and the duration of application [13].

Another result of exposing cells to electric pulses is the clustering of transmembrane proteins, forming pseudotunnel structures. This structural change enables molecules to pass through the cell membrane *(Fig. 2)* [11].

Beyond the impact of electrical pulses on cells, when exposed to tumor tissue, these pulses severely inhibit local blood perfusion to the point of almost complete cessation. This hemostatic effect provides a therapeutic advantage, particularly for tumors prone to bleeding. The anti-vascular characteristic of electrochemotherapy contributes to the therapy's antineoplastic activity [13].

Chemotherapeutic Drugs Used in Electrochemotherapy Bleomycin

This drug has a lipophobic structure, meaning it uses protein receptors to cross the cell membrane. Its primary mechanism of action is based on DNA lysis [11].

However, the lipophilic barrier of bleomycin makes it challenging to pass through via diffusion due to its

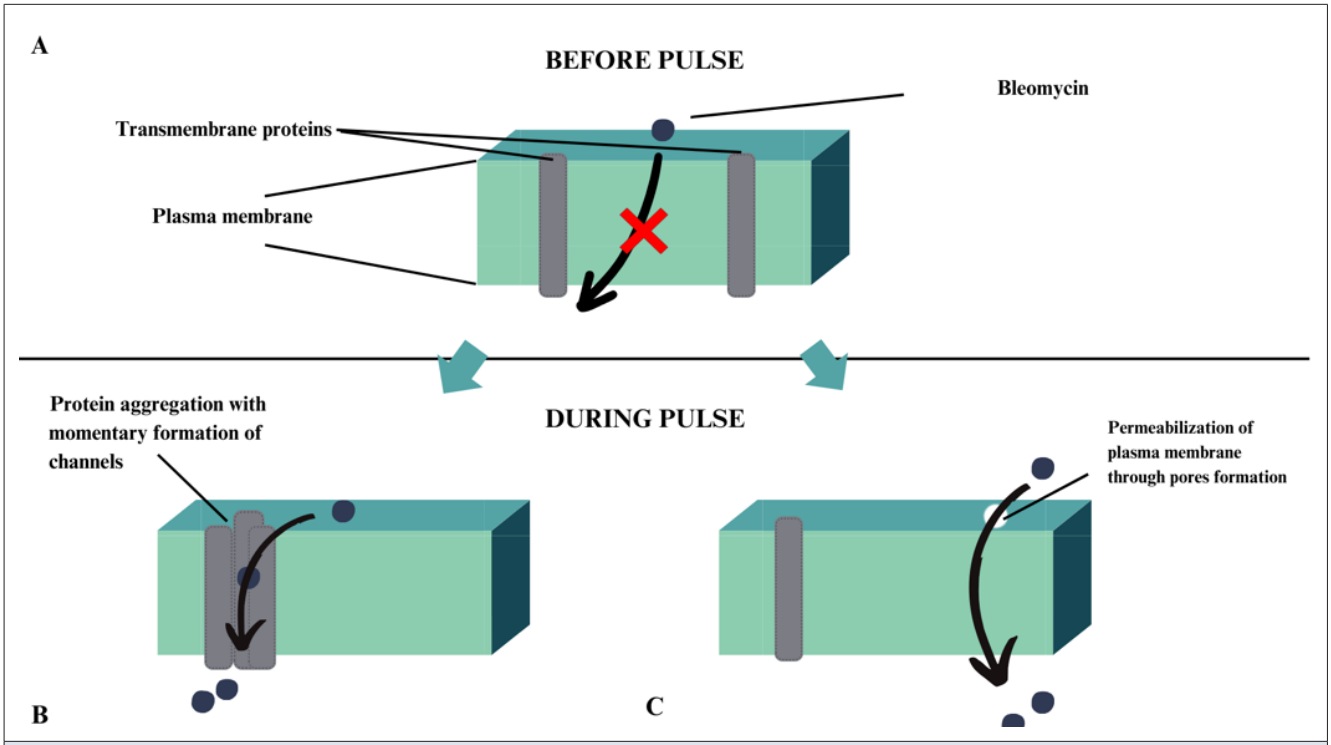

Fig 2. Mechanism of drug perfusion following electroporation. A) Cytoplasmic membrane before the application of permeabilizing pulses: the lipophobic drug cannot enter the cell without the intervention of a transmembrane carrier. B) The permeabilizing pulses induce clustering of transmembrane proteins and/or C) formation of pores in the lipid component of the membrane

lipophobic nature. Antineoplastic agents are typically taken into the cell through membrane protein carriers, but this process is quite limited and slow under standard conditions. The removal of these membrane receptors by tumor cells is one of their primary escape mechanisms, leading to chemotherapy resistance [14].

Preclinical studies suggest that with the assistance of electroporation, the cytotoxic effect of bleomycin can be potentiated 300-700 times [15].

Cisplatin

Cisplatin and its analogs interact with cancer cells by forming bonds with DNA bases, leading to the creation of DNA crosslinks, which ultimately result in cell death. The electroporation method can increase cisplatin's membrane permeability 4 to 8 times, allowing for the formation of more DNA crosslinks [10]. Mechanisms underlying cell resistance to cisplatin include the activation of DNA repair mechanisms and alterations in the dynamics of the molecule's intracellular and extracellular flow. Today, cisplatin is the second most commonly preferred chemotherapeutic agent in electrochemotherapy protocols [14].

Doxorubicin

Doxorubicin is one of the anthracycline class of chemotherapeutic agents with a multifaceted mechanism of action. These mechanisms include intercalation into DNA bases, breaking DNA strands, and inhibiting the topoisomerase II enzyme. Furthermore, it disrupts DNA replication by inhibiting DNA polymerase activity, causes changes in gene expression, and triggers the release of free radicals. Preclinical studies indicate that the effectiveness of doxorubicin on tumor cells can increase when used in combination with electrochemotherapy (ECT) in both *in vitro* and *in vivo* models [11].

Mitoxantrone

Mitoxantrone is a synthetic member of the anthracycline family. It is less harmful in terms of cardiotoxicity compared to other anthracycline compounds. Its mechanism of action is similar to that of doxorubicin. This drug is taken up into cells through diffusion according to the lipid component of the cell membrane. Studies in both human and veterinary medicine have observed that electrochemotherapy enhances the anti-tumor efficacy of mitoxantrone [14].

Clinical Cases on Electrochemotherapy in Birds

The summary of electrochemotherapy applications in some neoplasia cases in pet birds is presented in *Table 1*.

In the first case, a 10-year-old male budgerigar *(Melopsittacus undulatus)* presented to the clinic due to a non-healing exophytic mass on the left wing, which had been present for 2 months. A proliferative lesion on the wing measuring 2x1 cm was observed. During clinical

Table 1. Summarizes the outcomes achieved through ECT in the treatment of tumors of various histotypes in birds

Histotype	Species	Anatomical Region	Protocol	Drug	Treatment Response	Ref.
Epithelial hemangioendothelioma	Budgerigar *(Melopsittacus undulatus)*	Wing	8 pulses 1200 V/cm	Adjuvant to surgery ECT bleomycin IT	Complete response - 12 months	[16]
Cutaneous fibroma	Cockatiel *(Nymphicus hollandicus)*	Face	8 pulses 1300 V/cm	ECT cisplatin IT	Partial response – 3 years	[17]
Squamous Cell Carcinoma	Cockatiel *(Nymphicus hollandicus)*	Uropygial gland	8 pulses 1300 V/cm	ECT cisplatin IT and bleomycin IT	Complete response after last session – 18 months	[18]

ECT: Electrochemotherapy; IT: Intratumoral

examination, the bird's general condition was observed to be good, and it was interacting with its surroundings. Palpation of the wing caused noticeable discomfort in the bird, but other physical examination findings were normal. After hematological and radiological examinations, the mass was excised under anesthesia. Histopathological examination confirmed a diagnosis of incompletely excised low-grade epithelioid hemangioendothelioma due to the anatomical location and extent of the tumor, further surgical revision was not possible. In this context, adjuvant electrochemotherapy was chosen to enhance tumor control. The treatment protocol included intratumoral bleomycin application followed by two sessions of electropulsation at two-week intervals. No side effects were observed during treatment, and there was no tumor recurrence within 12 months postoperatively. The patient passed away after 12 months due to acute renal failure [16].

In the second case, an 11-year-old male cockatiel *(Nymphicus hollandicus)* presented to the clinic with a localized tissue mass located between the left eye and left nares. The mass measured 10 mm. During the clinical examination, the bird's overall condition was stable, but the tissue mass on its face was causing significant discomfort. An incisional biopsy was performed under gas anesthesia when fine-needle aspiration failed to obtain a sample. Histopathological examination revealed that the lesion was a fibroma. Due to the tumor's anatomical location, size, and infiltration into neighboring tissues, surgical excision was not recommended. As the initial treatment approach, antimicrobial and anti-inflammatory therapy was administered using marbofloxacin and meloxicam. Subsequently, imiquimod, an immunomodulatory agent with known antitumor properties, was topically applied once a day for 2 weeks. Due to an inadequate clinical response, a sisplatin-based electrochemotherapy protocol was initiated. After electrochemotherapy, necrotic tissue was shed in the first week, leaving a firm mass with a diameter of 7 mm. Over the next three months, no significant changes were observed in the size and morphology of the mass. This led to the need for a second electrochemotherapy session 12 weeks after the first treatment session. Following the second treatment session, a significant reduction in the size of the mass was observed, and it measured approximately 4 mm in diameter about a month later. From the second treatment session onwards, there was no increase in the size of the remaining tissue, and the bird's clinical condition was determined to be good after 3 years [17].

In the third case, a 12-year-old female cockatiel *(Nymphicus hollandicus)* was presented to the veterinary clinic with a diagnosis of squamous cell carcinoma in the uropygial gland localization. Electrochemotherapy was chosen as a minimally invasive treatment approach. In the first treatment session, electrochemotherapy with the use of cisplatin was administered. However, within the following month, no significant changes in tumor volume were observed. Subsequently, two electrochemotherapy sessions with bleomycin were performed at one-month intervals. After the second treatment session, positive responses were observed, including necrotic changes in the tumor and over 90% reduction in volume. Nevertheless, three months after the third treatment, tumor recurrence was detected. In this case, a fourth electrochemotherapy session based on bleomycin was conducted, resulting in complete tumor regression. Following this treatment, no progression of the tumor was observed during the 18-month period until the end of the patient's life [18].

CONCLUSION

Electrochemotherapy is playing an increasingly prominent role in the treatment of neoplasia in pet birds. Clinical studies have demonstrated that this treatment is effective both as an independent therapeutic approach and as adjuvant therapy. Patients have been observed to remain healthy for extended periods without recurrence after treatment. Notable side effects have been limited to minor muscle contractions during application. Electrochemotherapy, with its minimal invasiveness, effectiveness, and ease of application, has the potential to become a preferred treatment method in veterinary oncology. However, controlled, comprehensive studies are needed to determine the full efficacy and safety of electrochemotherapy. Such research could lay the groundwork for broader application in veterinary medicine.

DECLARATIONS

Availability of Data and Materials: Not applicable (As this article is a review of existing literature, no new datasets were generated or analyzed).

Conflict of Interest: The authors declared that there is no conflict of interest.

Declaration of Generative Artificial Intelligence (AI): The authors declare that the report and/or figures were not written/created by AI and AI-assisted technologies.

Author Contributions: Conceptualization, E.H.E. and S.Ö.; literature review, E.H.E.; writing-original draft preparation, E.H.E.; writing-review and editing, E.H.E. and S.Ö.; supervision, S.Ö. All authors have read and approved the final manuscript.

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