

# Surgical debulking and electrochemotherapy, including a tetrapolar single-needle electrode, are associated with clinical benefit in dogs with intranasal tumors

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## Objective

To evaluate the feasibility and preliminary clinical outcomes of surgical debulking combined with electrochemotherapy (ECT) using a multielectrode approach, including a tetrapolar single-needle electrode, in dogs with intranasal tumors.

## Methods

This retrospective observational study included client-owned dogs with intranasal tumors treated from 2017 through 2024 at a veterinary oncology referral center. Dogs were included if they underwent at least 1 surgical procedure combined with intraoperative bleomycin-based ECT using a multielectrode approach and had a minimum follow-up period of 2 months.

## Results

12 dogs were included, and most had advanced local disease (83% stages T3 to T4). Epithelial tumors predominated (91%), mainly adenocarcinoma (42%). Clinical response was observed in all dogs, including complete clinical response in 75% and partial clinical response in 25%. Local progression was documented by CT in 5 dogs (42%). Repeat procedures were performed in 67% of dogs because of persistent clinical signs or tumor progression. The median progression-free interval was 492 days, and the median survival time was 694 days. Treatment-related adverse events were frequent but predominantly mild to moderate, including partial wound dehiscence (50%), crust formation (42%), infection (25%), and oronasal fistula (25%). No procedure-related deaths occurred.

## Conclusions

Surgical debulking combined with ECT using a multielectrode approach, including a tetrapolar single-needle electrode, was feasible and associated with clinical benefit in dogs with intranasal tumors. These findings support further prospective investigation of this approach for intranasal tumors in dogs.

## Clinical Relevance

This approach may represent a treatment option for dogs with locally advanced intranasal tumors, particularly when radiotherapy is unavailable.

**Keywords:** bleomycin, debulking, electrochemotherapy, intranasal tumors, veterinary oncology

Intranasal tumors are relatively common in older dogs, accounting for approximately 1% to 2% of all cancers and 70% of chronic nasal diseases in this species.<sup>1</sup> These tumors are predominantly malignant,

clinically manifesting as epistaxis, sneezing, nasal discharge, and facial deformity.<sup>2</sup> Local disease progression represents a significant clinical challenge, often leading to extensive facial bone lysis and erosion of the cribriform plate. Due to the anatomical proximity between the nasal cavity and the brain, tumor progression may result in transcranial invasion. This can lead to neurological signs, such as seizures and behavioral changes.<sup>3</sup>

Therapeutic modalities described in the literature include palliative clinical approaches using

Received May 22, 2026

Accepted September 5, 2026

Published online September 17, 2026

doi.org/10.2460/javma.26.05.0387

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chemotherapy, NSAIDs, and toceranib as well as local therapies, which are more suitable for disease control.<sup>1</sup> Radiotherapy (RT) is considered the gold standard for the treatment of canine intranasal tumors. However, its high cost, limited availability, and need for multiple anesthetic sessions may restrict its use in clinical practice.<sup>4</sup> Another treatment option is surgery, which alone often provides limited long-term control due to the infiltrative nature of disease and the difficulty in achieving wide surgical margins.<sup>1,5</sup> Minimally invasive electrochemotherapy (ECT) has also been described as a treatment modality, primarily aiming to reduce tumor burden and improve clinical signs.<sup>6,7</sup>

Electrochemotherapy is a local antitumor treatment that combines the administration of hydrophilic chemotherapeutic agents (bleomycin, cisplatin) with the application of electrical pulses. These pulses generate an electric field that transiently increases cell membrane permeability, allowing higher intracellular drug uptake and resulting in enhanced cytotoxic effects with minimal systemic toxicity.<sup>8</sup> The increasing use of this treatment in veterinary medicine reflects several advantages, including efficacy, relatively low cost, selectivity for tumor cells and low treatment-related morbidity.<sup>9,10</sup> Electrochemotherapy has been used for the treatment of oral,<sup>11,12</sup> bladder,<sup>13</sup> and skin tumors in small-animal oncology, including squamous cell carcinoma,<sup>14,15</sup> soft tissue sarcomas,<sup>16,17</sup> and mast cell tumors.<sup>18,19</sup> Although ECT alone can achieve good local control, its efficacy may be limited in larger lesions. In such cases, surgical debulking can reduce tumor volume, potentially improving electric field distribution and treatment efficacy.<sup>8</sup>

To the best of our knowledge, no clinical studies have evaluated the outcomes of combining surgery and ECT for intranasal tumors in dogs. Only an isolated case report<sup>20</sup> involving a chemoresistant transmissible venereal tumor has been described, which differs in biological behavior from tumors typically affecting the nasal cavity. In addition, a major challenge in the treatment of tumors located within bony cavities is the generation of a sufficient electric field to ensure reversible electroporation, which may not be achieved using standard electrodes (plate or needle arrays) due to the insulating properties (ie, very low conductivity) of bone and the presence of air, leading to electric field distortion.<sup>20,21</sup> To overcome this limitation, our group has incorporated a tetrapolar single-needle electrode designed for use in bony cavities. This electrode is capable of generating a circular electric field with a diameter of 3 mm, with electrical parameters compatible with standard ECT protocols and commercially available electroporators as previously described.<sup>21</sup>

We hypothesized that the combination of surgery and ECT using a single-needle electrode would have a synergistic effect, improving local tumor control while maintaining low treatment-related morbidity in dogs with intranasal tumors. The aim of this retrospective study was to evaluate the feasibility and preliminary clinical outcomes of this novel therapeutic approach.

## Methods

### *Study design*

This retrospective original research included canine patients treated at the oncology service of Vet Câncer Clinic, São Paulo, Brazil, from 2017 through 2024 that underwent surgery combined with ECT for intranasal tumors. The medical records of eligible patients were reviewed, and cases were included if they had undergone at least 1 surgical procedure combined with intraoperative ECT using a multielectrode approach (plate electrodes, needle electrodes, or a single-needle electrode) and had a minimum follow-up period of 2 months, allowing assessment of adverse events and documented clinical response. Cases with insufficient medical records or follow-up shorter than 2 months were excluded.

### *Treatment*

A complete preoperative evaluation was performed, including hematological and biochemical analyses to assess renal and hepatic function as well as coagulation status. The animals were also subjected to echocardiography and electrocardiography. Thoracic radiographs and abdominal ultrasonography were used to investigate the presence of metastasis. Contrast-enhanced CT of the skull was performed in all dogs for surgical planning and disease staging according to the modified Adams staging system.<sup>22</sup> Regional lymph nodes, bone involvement, and evidence of intracranial extension were also assessed during CT examination. Stage T1 was tumor confined to 1 nasal passage or frontal sinus with no bony involvement. Stage T2 was tumor involving bone with no orbital, SC, submucosal, or nasopharyngeal mass. Stage T3 was tumor involving the orbit or presence of an SC or submucosal mass. Stage T4 was tumor causing cribriform plate destruction.

All dogs underwent surgical debulking followed by ECT. Surgical access was obtained either through a bilateral dorsal rhinotomy or a partial maxillectomy, depending on tumor location and extension, with the aim of providing adequate exposure of the nasal cavity and complete visualization of the lesion. For dorsal rhinotomy, the incision was performed over the area of greatest tumor involvement, allowing direct access to the nasal cavity. A nasal bone flap was created and removed to provide surgical access and was not replaced following tumor debulking. In dogs presenting with facial deformity caused by the tumor, the surgical approach was centered over the affected region. Partial maxillectomy, with or without canine tooth extraction, provided wide lateral access to the affected nasal cavity and was indicated in cases in which the neoplasm extended to the middle third of the ipsilateral nasal cavity. Following partial maxillectomy, communication between the oral and nasal cavities was intentionally maintained to facilitate postoperative monitoring of the surgical site. In dogs requiring repeated procedures because of tumor progression or persistence of clinical signs, the same surgical access site was used.

In both surgical approaches, gross tumor debulking was performed after adequate access to the

nasal cavity had been achieved to remove macroscopically visible neoplastic tissue and was immediately followed by ECT. Intraoperative hemorrhage was controlled using monopolar electrocautery and direct compression with sterile gauze. Bleomycin was diluted in 5 mL of saline solution and administered IV at a dose of 15,000 IU/m<sup>2</sup>. After an 8-minute interval, a set of 8 electrical pulses of 100- $\mu$ s duration at a frequency of 1 to 5,000 Hz was delivered using either a BTX ECM 830 electroporator (Harvard Apparatus) or E-Pore system (MMMR Equipamentos e Tecnologia). All dogs underwent electroporation using 3 complementary electrode types to achieve adequate coverage of the surgical bed and the irregular surfaces of the nasal cavity. Standard needle (arrow) and plate electrodes were applied through the surgical approach to ensure adequate coverage of the exposed surgical bed. The tetrapolar single-needle electrode was applied through the surgical approach and, when necessary, through the nostril to electroporate regions that could not be adequately reached through the surgical access alone. Electrode positioning was guided by direct intraoperative visualization to ensure adequate coverage of the accessible nasal cavity, including the cribriform plate region. Preoperative CT was used to determine the maximum insertion depth of the tetrapolar single-needle electrode, thereby preventing inadvertent penetration beyond the intended treatment area. Electric fields of 1,000 V/cm and 1,300 V/cm were applied with the standard needle and plate electrodes, respectively, whereas the tetrapolar single-needle electrode was operated at an applied voltage of 500 V.<sup>21</sup> Regardless of the electrode type, sterile conductive gel was applied throughout the nasal cavity to ensure uniform and effective contact with its irregular surfaces. After completion of electroporation, the conductive gel was gently removed from the surgical site. Electroporation was performed within a therapeutic window of 8 to 28 minutes following bleomycin administration as recommended by Tellado et al.<sup>8</sup>

### Follow-up

The patients were followed according to a standardized schedule. They were reevaluated 3 days after the procedure and subsequently once weekly until completing 1 month. After the first month, evaluations were performed every 2 weeks until 2 months after the procedure. Thereafter, patients were assessed every 2 months until completing 1 year of follow-up. After this period, the follow-up schedule was individualized.

Owners were instructed to return to the oncology service if any clinical signs suggestive of tumor recurrence were observed. At each follow-up visit, clinical signs were recorded. The predefined signs considered indicative of possible tumor recurrence included nasal bleeding, serosanguineous nasal discharge, respiratory difficulty, sneezing with discharge, signs of pain, and decreased appetite. Follow-up CT scans were performed according to the clinician's assessment and with owner consent.

### Adverse events

Adverse events were assessed and graded according to the Veterinary Cooperative Oncology Group-Common Terminology Criteria for Adverse Events version 2<sup>23</sup> as follows: grade 1 (mild), grade 2 (moderate), grade 3 (severe or medically significant but not immediately life-threatening), grade 4 (life-threatening consequences), and grade 5 (death related to adverse events).

### Treatment response

Response to treatment was assessed based on owner-reported history and clinical examination performed at the treatment center 6 to 8 weeks following ECT using clinical response criteria adapted from Hayes et al<sup>24</sup> originally described for RT response assessment. Because follow-up CT was not systematically performed in all dogs, treatment response was evaluated based on clinical improvement rather than objective imaging-based tumor response. Complete clinical response (CCR) was defined as complete resolution of clinical signs associated with the nasal tumor, including restoration of nasal airflow and disappearance of previous signs, such as sneezing, epistaxis, nasal discharge, mouth breathing, dyspnea, epiphora, facial swelling, facial pain, cough, exophthalmos, or neurological abnormalities. Partial clinical response (PCR) was defined as persistence of 1 or more clinical signs with overall clinical improvement. Progressive clinical disease was defined as worsening of existing clinical signs or development of new clinical signs attributable to the nasal tumor.

### Statistical analysis

All collected data were reported using descriptive statistics due to the small number of cases. Median survival time (MST) was defined as the interval from the date of surgery to disease-related death. Progression-free interval (PFI) was defined as the time from the date of surgery to the first occurrence of clinical disease progression or disease-related death. Patients that died from confirmed causes unrelated to the nasal tumor or were alive at the end of the study period were censored. Overall median PFI and MST were estimated using the Kaplan-Meier method. Owing to the small sample size, survival outcomes stratified by clinical variables are presented for descriptive purposes only, with subgroup-specific MSTs calculated as simple descriptive medians rather than Kaplan-Meier estimates. No statistical comparisons between subgroups were performed. The data were analyzed using R (version 4.3.3; R Foundation for Statistical Computing).

## Results

### Patient data and tumor features

A total of 12 dogs with intranasal tumors treated with ECT were included in this retrospective study. The median age at diagnosis was 11 years (range, 4 to 14 years). There was an equal sex distribution, with 6 males and 6 females. The breeds represented included Border Collie (n = 1), Golden Retriever (2), Dachshund (2), mixed-breed dogs (3), Cocker

Spaniel (1), Pit Bull (1), German Shepherd (1), and Maltese (1).

The presenting clinical signs included epistaxis (9 of 12 [75%]), sneezing (5 of 12 [42%]), and facial deformity (5 of 12 [42%]). Less commonly reported signs included seizures in 1 dog and ocular abnormalities in another dog, including ocular discharge, hyphema, and proptosis.

Pretreatment diagnosis was obtained in 9 dogs, either by cytology (5 of 9 [56%]) or rhinoscopy-guided biopsy (4 of 9 [44%]). Definitive histopathological diagnosis was ultimately obtained in all dogs from intraoperative samples collected during the debulking surgery and ECT procedure. Adenocarcinoma was the most frequent histologic diagnosis (5 of 12 [42%]), followed by transitional carcinoma (3 of 12 [25%]). Additional diagnoses included 1 nasal squamous cell

carcinoma, 1 ameloblastoma with carcinoma, and 1 neoplasm reported as adenoid cystic carcinoma. One dog was diagnosed with chondrosarcoma. Overall, epithelial tumors accounted for 11 of 12 cases (92%).

Preoperative CT was performed in all dogs. According to the Adams staging system, most dogs presented with advanced local disease at the time of diagnosis. Two dogs (17%) were classified as stage T2, 3 (25%) as stage T3, and 7 (58%) as stage T4. Overall, 10 of 12 dogs (83%) had locally advanced tumors (T3 to T4). No imaging findings suggestive of regional lymph node metastasis were identified on CT. One dog presenting with neurological signs underwent brain MRI, which revealed a primary frontal lobe tumor unrelated to the intranasal neoplasm. Thoracic radiography and abdominal ultrasonography did not reveal evidence of distant metastasis in any dog at the time of staging.

### Toxicity evaluation

No dogs died during the surgical procedure, ECT treatment, or immediate postoperative period.

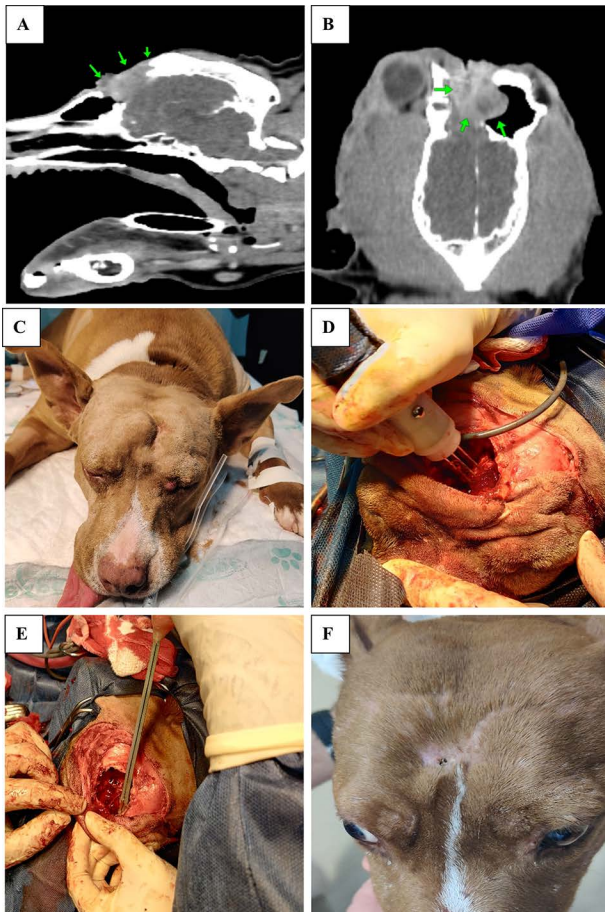


**Figure 1**—Dog with stage IV nasal chondrosarcoma (case 9) treated with surgical debulking and electrochemotherapy via a dorsal rhinotomy approach. Pretreatment CT images in sagittal (A) and dorsal (B) planes demonstrating a mass involving the frontal sinus with lysis of the cribriform plate. C—Image obtained on the day of the procedure showing facial deformity due to frontal sinus involvement. Intraoperative images following dorsal rhinotomy and tumor debulking with electrochemotherapy performed using needle-array electrodes (D) and single-needle electrode (E). F—Postoperative image after suture removal demonstrating complete healing and improved facial deformity.

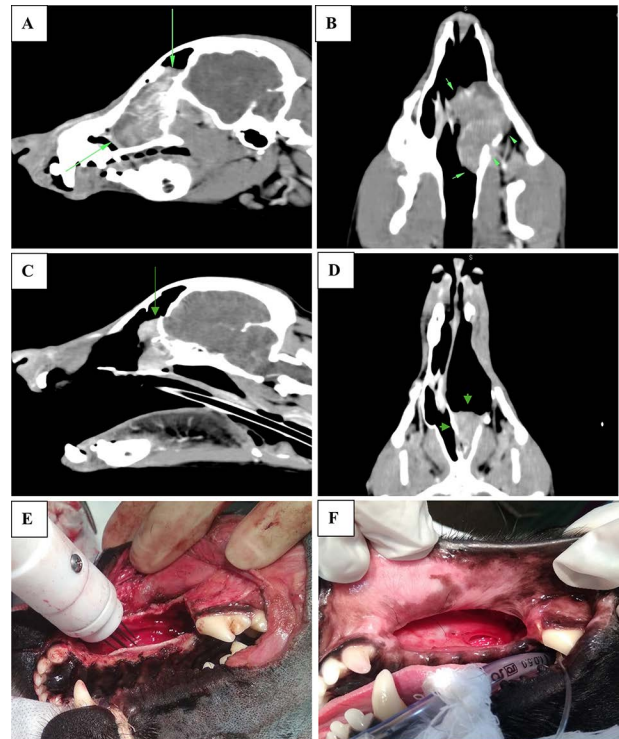


**Figure 2**—Dog with stage III nasal adenocarcinoma (case 3) treated with surgical debulking and electrochemotherapy via a maxillectomy approach. Pretreatment CT images in sagittal (A) and dorsal (B) planes demonstrating a mass in the left nasal cavity, extending to the right side, with extensive bone lysis and nasopharyngeal obstruction. Posttreatment CT images in sagittal (C) and dorsal (D) planes obtained 100 days after ECT showing a favorable response with reduced involvement of the frontal sinus and no progression of osteolysis. E—Intraoperative image demonstrating electrochemotherapy using needle-array electrodes following tumor debulking. F—Image obtained at the second ECT session, 129 days after the first, showing persistence of a large oronasal fistula.

Adverse events included sneezing (grade 1;  $n = 1$ ), crust formation (grade 1; 5), serosanguinous nasal discharge (grade 1; 2), partial wound dehiscence (grade 2; 6), oronasal fistula (grade 1; 3), infection (grade 2; 3; including 1 infraorbital abscess), SC emphysema (grade 1; 1), edema (grade 1; 1), and skin ulceration (grade 2, 1; grade 3, 2).

Crust formation, sneezing, serosanguinous nasal discharge, edema, and SC emphysema were transient adverse events. Dogs with oronasal fistula did not exhibit clinical signs or complications related to the defect, and the condition was well tolerated. Infections were treated with antibiotic therapy and local wound care. Although adverse events occurred relatively frequently, they were predominantly grade 1 or 2 in severity, were managed with conservative treatment, and did not negatively affect the dogs' quality of life according to owner reports.

### Treatment response and follow-up

Surgical access was obtained via dorsal rhinotomy (**Figure 1**) in 8 of 12 cases (67%) and via partial maxillectomy (**Figure 2**) in 4 of 12 (33%). All dogs

experienced clinical improvement following treatment, including 9 CCR (75%) and 3 PCR (25%). Clinical benefit was observed in all dogs and most commonly consisted of complete resolution or marked improvement of clinical signs. Among dogs that achieved a CCR, most had T4 lesions (5 of 9 [56%]), whereas 2 dogs (22%) had T2 lesions, and 2 (22%) had T3 lesions. Of the 3 dogs with a PCR, 2 had T4 lesions, and 1 had a T3 lesion.

Local progression was documented by CT in 5 dogs (42%), whereas progression was suspected based on clinical assessment in 2 additional dogs (17%) without imaging confirmation. Among the 5 dogs with CT-documented progression, 2 had previously achieved a CCR and subsequently developed recurrence of clinical signs, whereas 3 developed new lesions identified on follow-up CT.

Regarding the number of procedures, 4 of 12 dogs (33%) underwent a single procedure, 5 of 12 (42%) underwent 2 procedures, and 3 of 12 (25%) underwent 3 procedures because of disease progression or persistence of clinical signs. All additional procedures consisted of repeat surgical debulking

**Table 1**—Clinical characteristics and outcomes of dogs with intranasal tumors treated with surgical debulking and electrochemotherapy.

| Case | Adams stage | Diagnosis | Surgery | Procedures | Electrodes used          | Adverse events (VCOG-CTCAE v2)                                                      | Treatment response | Systemic treatment                           | PFI (d) | Recurrence/progression | MST (d) | Tumor-related death |
|------|-------------|-----------|---------|------------|--------------------------|-------------------------------------------------------------------------------------|--------------------|----------------------------------------------|---------|------------------------|---------|---------------------|
| 1    | T2          | TC        | DR      | 1          | Needle + PI + tetrapolar | Sneezing (grade 1), crusting (grade 1)                                              | CCR                | No                                           | 2,051   | No                     | 2,051   | No (alive)          |
| 2    | T2          | CA        | PM      | 1          | Needle + PI + tetrapolar | Partial dehiscence (grade 2), oronasal fistula (grade 1)                            | CCR                | No                                           | 1,156   | No                     | 1,156   | No                  |
| 3    | T3          | AC        | PM      | 3          | Needle + PI + tetrapolar | Oronasal fistula (grade 1), partial dehiscence (grade 2)                            | PCR                | No                                           | 526     | Yes (CT)               | 526     | Yes                 |
| 4    | T4          | AC        | PM      | 2          | Needle + PI + tetrapolar | Oronasal fistula (grade 1), partial dehiscence (grade 2), skin ulceration (grade 3) | CCR                | No                                           | 335     | Yes (CT)               | 415     | Yes                 |
| 5    | T3          | AC        | DR      | 1          | Needle + PI + tetrapolar | Partial dehiscence (grade 2), skin ulceration (grade 3)                             | CCR                | No                                           | 787     | No                     | 787     | No (alive)          |
| 6    | T4          | TC        | DR      | 2          | Needle + PI + tetrapolar | Edema (grade 1), partial dehiscence (grade 2), SC emphysema (grade 1)               | CCR                | Toceranib phosphate (Palladia) and piroxicam | 287     | Yes (CT)               | 543     | Yes                 |
| 7    | T4          | AC        | DR      | 1          | Needle + PI + tetrapolar | Serosanguinous nasal discharge (grade 1)                                            | PCR                | No                                           | 148     | No                     | 148     | No                  |
| 8    | T4          | ACC       | DR      | 2          | Needle + PI + tetrapolar | Serosanguinous nasal discharge (grade 1)                                            | CCR                | No                                           | 1497    | No                     | 1,497   | No                  |
| 9    | T4          | CSA       | DR      | 2          | Needle + PI + tetrapolar | Crusting (grade 1), skin ulceration (grade 2)                                       | CCR                | Toceranib phosphate (Palladia)               | 492     | Yes (CT)               | 492     | No                  |
| 10   | T3          | AC        | DR      | 2          | Needle + PI + tetrapolar | Crusting (grade 1), partial dehiscence (grade 2), infection (grade 2)               | CCR                | Metronomic cyclophosphamide                  | 71      | Yes (clinical)         | 694     | Yes                 |
| 11   | T4          | SCC       | PM      | 3          | Needle + PI + tetrapolar | Infection (grade 2), partial dehiscence (grade 2), crusting (grade 1)               | PCR                | No                                           | 30      | Yes (clinical)         | 143     | Yes                 |
| 12   | T4          | TC        | DR      | 3          | Needle + PI + tetrapolar | Crusting (grade 1), infection (grade 2)                                             | CCR                | No                                           | 85      | Yes (CT)               | 204     | Yes                 |

Yes (CT) indicates progression documented by CT, whereas yes (clinical) indicates progression suspected based on clinical assessment without imaging confirmation.

AC = Adenocarcinoma. ACC = Adenoid cystic carcinoma. CA = Carcinoma with ameloblastoma. CR = Complete clinical response. CSA = Chondrosarcoma. DR = Dorsal rhinotomy. MST = Median survival time. PFI = Progression-free interval. PI = Plate Electrode. PM = Partial maxillectomy. PR = Partial clinical response. SCC = Squamous cell carcinoma. TC = Transitional carcinoma. VCOG-CTCAE v2 = Veterinary Cooperative Oncology Group–Common Terminology Criteria for Adverse Events version 2.

followed by ECT. Adjuvant therapy was administered in 4 dogs, including toceranib phosphate (Palladia) in 2 dogs, metronomic cyclophosphamide in 1 dog, and piroxicam in 1 dog. Clinical characteristics of the cases are presented in **Table 1**.

### Survival analysis

At the end of the study period, 2 dogs were alive (17%), and 10 had died (83%). Among the deceased dogs, 6 died due to local tumor progression and were considered events in the survival analysis. Four dogs

died from confirmed causes unrelated to the nasal tumor and were censored, including 1 dog with a primary frontal lobe brain tumor, 1 with pulmonary thromboembolism, and 2 euthanized because of advanced age, severe mobility impairment, and poor quality of life in the absence of clinical evidence of tumor progression.

Overall, the median PFI was 492 days (95% CI, 287 days to not reached), and the MST was 694 days (95% CI, 526 to not reached), according to the Kaplan-Meier analysis shown in **Figure 3**. Survival

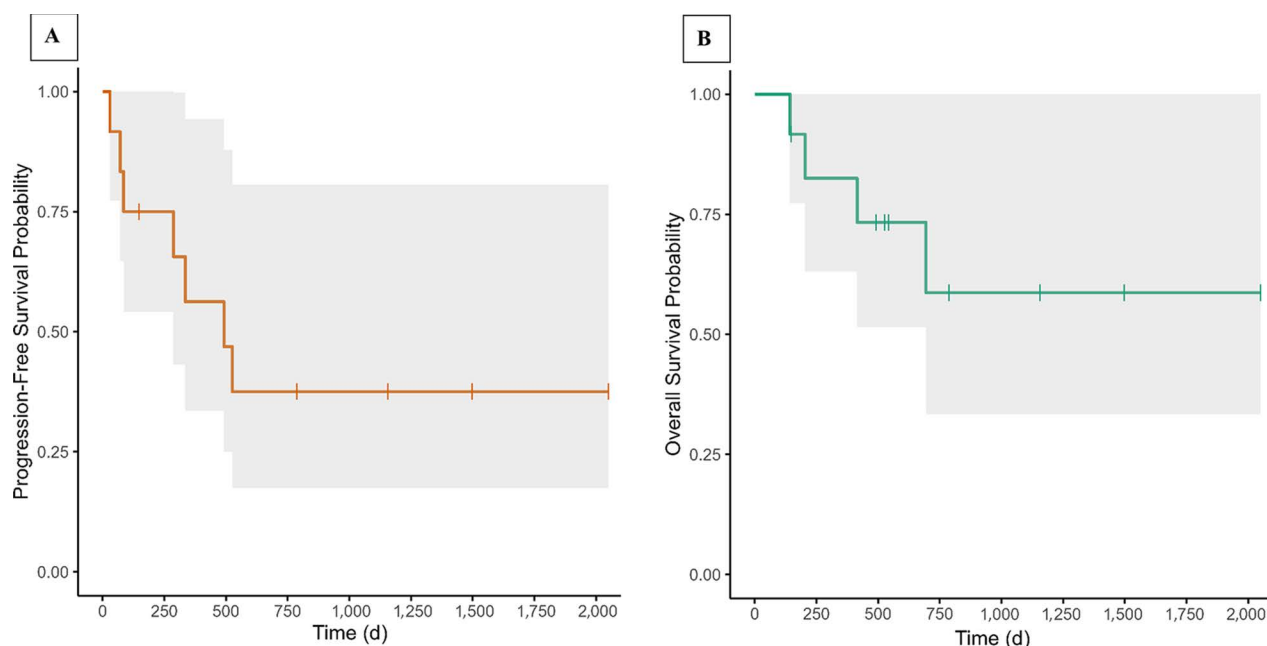


**Figure 3**—Kaplan-Meier survival curves for progression-free interval and median survival time. A—Progression-free interval over time (days) with a median of 492 days (95% CI, 287 days to not reached). B—Overall survival time (days) with a median of 694 days (95% CI, 526 to not reached). Tick marks indicate censored observations. Shaded areas represent 95% CIs.

**Table 2**—Descriptive survival outcomes according to clinical variables in dogs with nasal tumors treated with surgical debulking and electrochemotherapy.

| Variables                | n | PFI (d; range)    | MST (d; range)    |
|--------------------------|---|-------------------|-------------------|
| Tumor stage              |   |                   |                   |
| T2/T3                    | 5 | 787 (71–2,051)    | 787 (526–2,051)   |
| T4                       | 7 | 287 (30–1,497)    | 415 (143–1,497)   |
| Tumor response           |   |                   |                   |
| CR                       | 9 | 492 (71–2,051)    | 694 (204–2,051)   |
| PR                       | 3 | 148 (30–526)      | 148 (143–526)     |
| No. of procedures        |   |                   |                   |
| 1                        | 4 | 971 (148–2,051)   | 971 (148–2,051)   |
| 2                        | 5 | 335 (71–1,497)    | 543 (415–1,497)   |
| 3                        | 3 | 85 (30–526)       | 204 (143–526)     |
| Tumor progression        |   |                   |                   |
| No                       | 5 | 1,156 (148–2,051) | 1,156 (148–2,051) |
| Yes                      | 7 | 186 (30–526)      | 470 (143–694)     |
| Final status             |   |                   |                   |
| Alive                    | 2 | 1,419 (787–2,051) | 1,419 (787–2,051) |
| Dead (other causes)      | 4 | 824 (148–1,497)   | 824 (148–1,497)   |
| Dead (tumor progression) | 6 | 186 (30–526)      | 470 (143–526)     |

All survival data stratified by clinical variables are presented for descriptive purposes only. In particular, survival according to the number of procedures should not be interpreted as a prognostic comparison because of the potential for immortal time bias.

CR = Complete response. PR = Partial response.

analysis according to stage, tumor response, number of procedures, tumor progression, and final status is described in **Table 2**.

## Discussion

This retrospective study is the first to evaluate, in a cohort of dogs, surgical debulking followed by ECT using a multielectrode approach (needle, plate, and tetrapolar single-needle electrodes) with conductive gel for the treatment of intranasal tumors. While recent reports<sup>7</sup> have described the feasibility of endoscopic-guided ECT as a minimally invasive strategy for canine nasal tumors, this study differs by combining ECT with surgical debulking and a multielectrode approach specifically designed to overcome the anatomical and electrical challenges of the nasal cavity. The tetrapolar single-needle electrode was used to treat anatomically restricted regions that could not be adequately reached with conventional needle and plate electrodes, which were applied to more accessible areas. This approach resulted in clinical benefit in all dogs and an MST of 694 days despite the majority of patients (83.3%) presenting with locally advanced disease (T3 to T4).

The MST of 694 days is comparable to that reported for RT, which remains the standard of care for canine intranasal tumors. Definitive RT protocols report MSTs ranging from 347 to 641 days, whereas palliative protocols range from 146 to 512 days.<sup>25–27</sup> Similar outcomes have been reported with stereotactic RT (MST of 388 to 586 days).<sup>3,28,29</sup> However, direct comparison between these studies should be interpreted with caution because of the retrospective design, small sample size, heterogeneous case population, inconsistent imaging follow-up, and lack of a control group in this study. In addition, the combination of definitive RT and surgical cytoreduction has been associated with substantially longer survival than RT alone in selected dogs, with median survival approaching 3 years (approx 1,095 days).<sup>25</sup> Despite these advantages, RT requires multiple treatment sessions (3 to 20 anesthetic events), is associated with high costs, and remains unavailable in many veterinary centers, whereas the approach described here required only 1 to 3 procedures.

Surgery alone for intranasal tumors is associated with an MST of 3 to 6 months following a single surgical procedure without chemotherapy or other adjuvant therapy,<sup>30</sup> mainly due to the difficulty of achieving tumor-free margins without significant mutilation. Surgical debulking reduces the macroscopic tumor burden but invariably leaves residual disease. Electrochemotherapy may address this limitation by targeting residual disease as suggested by the longer MST observed in this study (694 days vs 3 to 6 months with surgery alone).

A previous study by Maglietti et al<sup>6</sup> demonstrated encouraging results using ECT alone with a single-needle electrode, reporting an MST of 16.5 months and an objective response rate of 91%. However, direct comparison with this study should be interpreted cautiously because the populations differed substantially regarding disease stage. In that

study, 64% of dogs had T1 to T2 tumors, and only 18% had T4 disease, whereas 83.3% of dogs in our cohort presented with locally advanced disease (T3 to T4), including 58.3% classified as T4. Therefore, although survival outcomes were comparable, these findings demonstrate that the combination of surgical debulking and intraoperative ECT is feasible and associated with favorable clinical outcomes even in a cohort composed predominantly of dogs with advanced local disease.

The application of ECT in bony cavities is challenging due to the insulating properties of bone and the distortion of the electric field caused by air.<sup>20</sup> Conventional electrodes, such as plate and needle-array electrodes, may fail to adequately cover anatomically constrained regions, particularly the ventral meatus and “floor corners” of the nasal cavity, resulting in areas of insufficient electric field distribution (“blind spots”). The tetrapolar single-needle electrode used in this study was specifically designed to address these limitations by allowing insertion through the nostril and generation of a circular and homogeneous electric field in narrow anatomical regions. However, given the complex 3-D anatomy of the nasal cavity, the tetrapolar electrode was used in combination with conventional needle and plate electrodes to ensure comprehensive treatment coverage. Needle electrodes were used in areas with a higher presence of soft tissues, where direct intralésional penetration was feasible. Plate electrodes were applied in regions adjacent to bone where it was viable to distribute the electric field despite the anatomical limitations imposed by the bone surfaces. The tetrapolar single-needle electrode was specifically employed to cover blind spots where the other electrodes could not adequately distribute the electric field. Combined with conductive gel, this multielectrode approach may improve electric field homogeneity and facilitate electroporation coverage in areas that are difficult to access using any single electrode type alone.<sup>20,31,32</sup> These characteristics are illustrated in **Figure 4**. Previous experimental and computational investigations involving oral tumors, bone-associated tumors, and nasal cavity applications demonstrated that tissue heterogeneity, electrode geometry, and the presence of bone or air interfaces may significantly influence treatment efficacy and electric field homogeneity.<sup>20,32–35</sup>

Local progression was documented by CT in 5 dogs (42%), and progression was suspected based on clinical assessment in 2 additional dogs (17%). These findings are within the range of local progression rates reported for RT (58% to 72%).<sup>29,36</sup> The possibility of repeated ECT application (42% of dogs underwent 2 procedures and 25% 3 procedures) suggests that retreatment is feasible, potentially with lower cumulative toxicity compared to reirradiation.<sup>4,37,38</sup> In this study, complications associated with surgical debulking combined with ECT were frequent; however, most were mild to moderate and transient (eg, sneezing, SC emphysema, edema, crust formation, infection, and serosanguineous nasal discharge). Even in dogs that developed oronasal fistulas, a

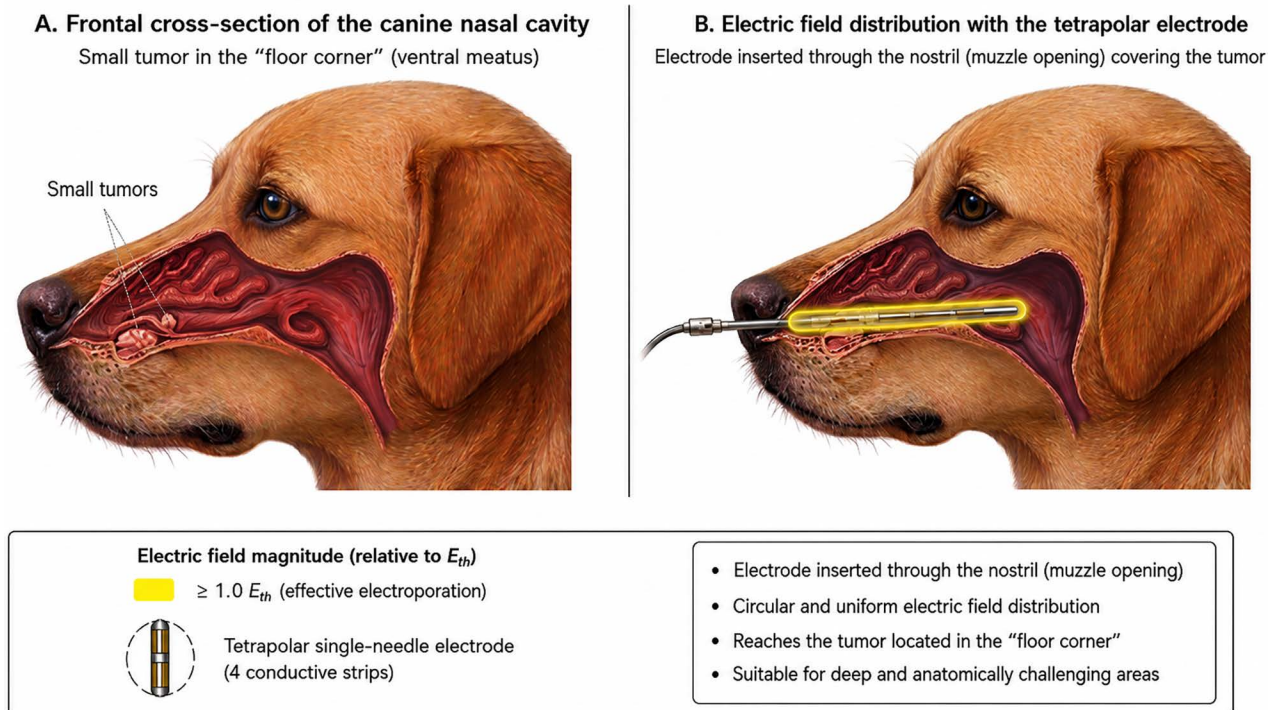


**Figure 4**—Schematic representation of electric field coverage within the canine nasal cavity during electrochemotherapy. A—Parasagittal cutaway view of the left nasal and pharyngeal regions demonstrating small tumors located in the ventral meatus (“floor corner”), an anatomically challenging region for conventional plate or needle-array electrodes. Due to the complex anatomy of the nasal cavity, conventional electrodes may fail to generate adequate electric field distribution in these areas, resulting in regions of insufficient field coverage (“blind spots”). B—Illustration of the tetrapolar single-needle electrode inserted through the nostril (muzzle opening), generating a circular and homogeneous electric field capable of covering tumors located in anatomically restricted regions of the nasal cavity. The tetrapolar electrode may improve electric field distribution in areas where conventional electrodes cannot be adequately positioned because of anatomical constraints.  $E_{th}$  = Electroporation threshold electric field. Figure 4 was generated using Gemini 3.1 Pro (Google LLC) based on the authors’ original concept and specifications.

complication that could potentially result in morbidity and require surgical correction, no associated clinical signs were observed. Therefore, these findings suggest that, under the conditions evaluated, this treatment approach was well tolerated and feasible.

It is also important to acknowledge that the early improvement in clinical signs observed in this study was likely influenced by surgical debulking itself, which immediately reduced tumor burden and relieved local obstruction. Because all dogs underwent combined treatment, the individual contributions of surgical debulking and ECT to the initial clinical response cannot be distinguished. Nevertheless, the prolonged survival observed in this cohort likely reflects the effect of ECT on residual microscopic disease following cytoreductive surgery. Owing to the retrospective design and the absence of a control group, however, the individual contribution of each treatment modality to survival cannot be determined. Therefore, the favorable outcomes observed in this study should be interpreted as the result of the combined therapeutic approach.

The main limitations of this study include its retrospective nature, nonrandomized design, lack of a control group, small sample size ( $n = 12$ ), and heterogeneous tumor population, including variation in tumor stage and histological subtype, all of which may

have influenced treatment response and survival outcomes. Treatment response was primarily assessed clinically because follow-up CT was not systematically available; therefore, clinical response should not be interpreted as equivalent to complete tumor response. Similarly, because follow-up CT examinations were not performed systematically, PFI was primarily based on clinical evidence of disease progression, which may have underestimated subclinical tumor progression. Adjuvant systemic therapy was administered to a subset of dogs ( $n = 3$ ), representing a potential confounding factor; therefore, survival in these cases cannot be attributed exclusively to surgical debulking combined with ECT. The criteria for repeating treatment were not standardized and were based on clinical judgment, including persistence of clinical signs or evidence of disease progression. This may have introduced variability in treatment timing and outcome assessment. Because of the retrospective nature of the study, response assessment was heterogeneous, treatment-related toxicity may have been incompletely documented, and follow-up duration varied among dogs. Prospective, randomized studies with larger cohorts and standardized imaging follow-up are warranted.

This retrospective study demonstrated that the combination of surgical debulking and ECT, including

a tetrapolar single-needle electrode and conductive gel, is feasible and associated with clinical benefit in dogs with intranasal tumors. This approach targets residual disease following surgery in an anatomical region where achieving tumor-free margins is either unfeasible or would result in significant morbidity. Due to the limitations inherent to the retrospective design and the small sample size, prospective randomized studies are warranted to validate the efficacy and safety of this therapeutic approach.

## Acknowledgments

None reported.

## Disclosures

ChatGPT (GPT-5.6 Sol; OpenAI) was used as an assistive AI tool for language editing and revision of the manuscript under author supervision. No scientific content, data interpretation, references, or conclusions were generated by the tool. Google Gemini 3.1 Pro (Google LLC) was used to generate Figure 4, a descriptive schematic illustration of the ECT procedure, based on the authors' original concept and specifications. The authors reviewed and edited the AI-generated figure and take full responsibility for the integrity, accuracy, and scientific content of the figure and the final manuscript.

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## Funding

The research was funded by the authors' departments.

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