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CASE REPORT

# Intraoperative use of electrical impedance spectroscopy for adenoid cystic carcinoma of the lacrimal gland: A case report

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## Key Clinical Message

Electrical Impedimetric Tumor Detection System is a novel and promising tool for fast intraoperative tumor delineation and accurate safe margin detection in orbital tumors.

## Abstract

Adenoid cystic carcinoma (ACC) is a rare malignant tumor of epithelial origin, typically arising from the salivary and lacrimal glands. ACC is notorious for recurrence and a high rate of morbidity and mortality despite therapy. We presented a 48-year-old male patient with lacrimal gland ACC of the right orbit who underwent radical tumor resection and adjuvant radiotherapy. We applied a new diagnostic method, the Electrical Impedimetric Tumor Detection System, during surgery and tested its performance to enhance the precision of tumor resection. Two months after surgery, he underwent external radiation of 58 Gy in 29 fractions. He showed no tumor recurrence or metastasis in the 1-year follow-up visits. ITDS showed a precision of tumor and margin detection consistent with histopathology results. This novel ITDS may be a reliable system for fast intraoperative tumor delineation and accurate, safe margin detection in orbital tumors.

KEYWORDS

adenoid cystic carcinoma, cancer, electrical impedance spectroscopy, enucleation, surgery

## 1 | INTRODUCTION

Adenoid cystic carcinoma (ACC) is an uncommon malignant epithelial tumor that usually originates from the salivary and lacrimal glands. Orbital ACC is rare and commonly originates from the lacrimal gland.[1,2] ACC of the lacrimal gland accounts for 1.6% of all orbital tumors and is characterized clinically by periocular pain, ptosis, and/or proptosis, and inferomedial displacement of the globe.[3,4] It is associated with a slowly progressive course, local recurrence, perineural invasion, late distant metastasis, and poor outcomes.[5] Due to the rarity of LGACC, accurate diagnosis, treatment, and management are challenging.[6] A fast and reliable intraoperative method to detect tumor margins, assisting in removal of involved tissues and sparing uninvolved areas, has always been a potentially ideal method. So, we report a patient with ACC arising in the LG with proptosis of the right orbit. The main purpose of this paper is to show the utility of the novel electrical impedance spectroscopy (EIS) system for the surgical margin diagnosis of adenoid cystic carcinoma.

## 2 | CASE PRESENTATION

The patient was a 48-year-old man who was referred to the Farabi Hospital and Cancer Institute affiliated with Tehran University of Medical Sciences with progressive proptosis in the right eye. He complained of vague discomfort in the right periorbital area for 28 years, with progression in the last 5 years. The patient denied pain, paresthesia, diplopia, or other ophthalmologically associated symptoms. There was no history of redness, tearing, or photophobia. He also had no history of ocular surgery, eye trauma, exposure to chemicals, or radiation. The patient's medical history was not significant for hypertension, hyperthyroidism, or diabetes mellitus, and he did not use any medication. Orbital examination showed best-corrected visual acuity of 20/20 in both eyes, no relative afferent pupillary defect, normal extra-ocular movements, 5 mm of right non-axial proptosis measured using a Hertel exophthalmometer, and ptosis. Upper eyelid swelling with a hard, nontender mass on the orbital rim was palpable. The patient was alert and oriented, answered the questions appropriately, and had a normal mental status. A computed tomography (CT) scan showed a heterogeneous mass in the upper lateral of the right extraconal orbital compartment with a size of 30 × 17 mm and associated remodeling of the orbit's upper rim and bone erosion. Magnetic resonance imaging (MRI) showed a lobulated mass with dimensions of 32 × 25 × 26 mm at the superolateral aspect of the right orbital cavity with involvement of the levator and lateral rectus muscles (Figure 1). He did not show lymphadenopathy or metastasis on physical or radiological examinations. We considered this tumor T2N0M0 according to the American Joint Committee on Cancer (AJCC) edition 9.

Following a multidisciplinary tumor board, radical orbital exenteration and adjuvant radiotherapy were advised. Written informed consent was obtained from the patient before surgery for all diagnostic techniques applied by ITDS and for exenteration. In order to ensure thorough removal of the malignant margins as a companion technique to frozen pathology, the margins were evaluated intraoperatively by an electrical device called ITDS that had previously been developed (Figure 2). The measured $Z_{1kHz}$ and IPS of 1kΩ and −3.4 were similar to tumor responses in other carcinoma tissues and confirmed the malignant nature of the tumor. The ITDS data on the right orbital bone margin (2kΩ and −1.43 as the classification parameters of a suspicious region) was also matched with the frozen and later permanent pathology data (the superior margin was highly close to the tumor).

Postsurgical histological evaluation showed infiltration of neoplasia composed of abluminal basal and myoepithelial cells as well as luminal epithelial cells arranged in tubules and small cribriform nests (Figure 2A). Subsequent slide sectioning revealed that around 10% of the tumor is composed of well-demarcated islands of small hyperchromatic cells arranged in solid nests (Figure 2B). Foci of perineural and lymphovascular invasion are also identified; however, no bone erosion was detected.

Two months after surgery, the patient underwent external radiation of 58 Gy in 29 fractions, following the recommendation of our oncologist. The patient showed well-orbital granulation tissue and the epithelium lining with mild orbital socket and periorbital xerosis some months after the surgery. He showed no tumor recurrence or metastasis in the 1-year follow-up visits after the exenteration surgery.

## 3 | DISCUSSION

Progressive proptosis should be an alarm for the presence of rare tumors such as ACC. In a study on 23 cases of ACC, the most typical symptoms were proptosis in 20 (86.9%) cases.[7] Anjum et al. reported on univariate analysis that male gender, bone erosion, perineural invasion, solid histologic pattern, intracranial extension, and advanced tumor stage was an indicator of poor prognosis.[7] In our case, the histology pattern was cribriform with lymphovascular and perineural invasion without bone erosion, based on the frozen pathology report. Despite aggressive local treatment, LGACC shows a high rate of local recurrence and late distant metastasis, with significant resultant mortality.[8] Imaging is an essential diagnostic tool for presurgical evaluation in LG tumor cases.[9] Because of the rare nature of LGACC, a roadmap for the best possible

treatment must rely on retrospective data. To the best of our knowledge, no optimal treatment protocol for the management of ACC has been reported. The first conventional line of treatment consists of surgery, followed by postoperative radiotherapy.[10] This aligns with the decision made by our multidisciplinary tumor board. Taking the correct surgical approach to these lesions is probably one of the most critical management decisions and can save the patient from unnecessary morbidity and mortality.[11] Benelli and his colleagues have reported a 45-year-old man with involvement of the muscle (superior rectus) and neural invasion who finally underwent eye exenteration and adjuvant radiotherapy.[10] In our patient, the same as this study, radical orbital exenteration and adjuvant radiotherapy were considered due to muscle involvement and perineural invasion. A fast and reliable intraoperative method to detect tumor margins, assisting in the removal of involved tissues and sparing uninvolved areas, has always been a potentially ideal method. In this regard, the application of EIS in determining the tumoral nature of marginal tissues in breast cancer has been investigated.[12]

## 3.1 | Electrical Impedance Spectroscopy (EIS) application

Therefore, for the first time, we applied a new diagnostic method called ITDS during the surgery for ACC. This system works based on dielectric differences between normal and cancerous tissues arising from metabolic and pathophysiological changes that occur due to carcinogenesis. Impedimetric detection is performed using a handheld intraoperative ITDS, which extracts two classification parameters: Z1kHz (impedance magnitude at f = 1 kHz) and IPS (Impedance phase slope in the frequency range of 100 kHz–500 kHz) (Figure 3). These two parameters were previously introduced and evaluated in several projects to diagnose breast tumor margins, intraradiological breast tumor detection, and the diagnosis of involved lymph nodes in breast cancer patients.[13,14]

According to several types of research that have been conducted on tissue electrical equivalent circuits, Z1 kHz is a low-frequency parameter that reflects the extra-cellular matrix dielectric properties of the tissue, while IPS is a high-frequency parameter contributing to the dielectric properties of cell membranes and, to some extent, intracellular components. So, physical or metabolic changes that occur in cancerous cells (such as a greater nucleus-to-cytoplasm size ratio, more packing density of cells, metabolites produced through aerobic glycolysis, less stiffness of cytosol components (actin and tubulin), more membrane permeability, etc.), making these two parameters completely different in normal and tumoral tissues. In the present research, ITDS was used ex vivo as an observational complementary diagnostic device to evaluate the ocular tumor margin, which was a great match with

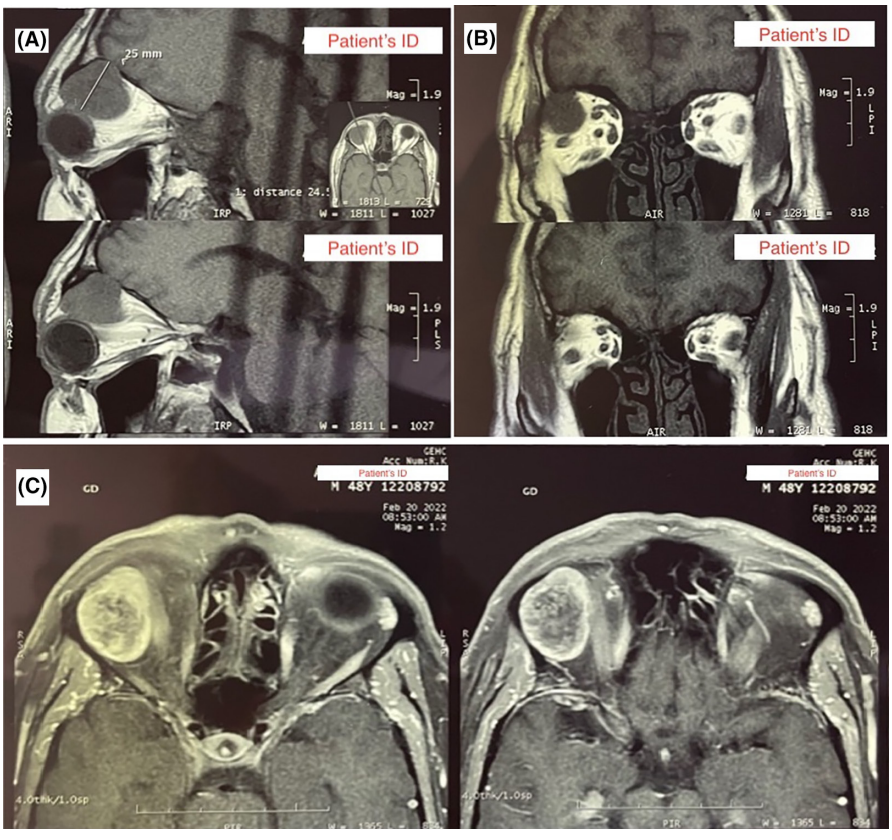


FIGURE 1 T1-weighted sagital(A) showing a 25 mm lesion in superior part of the right orbit involving periorbital fat, T1-weighted coronal(B) showing the periorbital fat and muscle, T1 weighted with gandolinium injection(C) showing enhancing lesion involving right lacrimla gland in right supralateral periorbital area with involvement of periorbita.

frozen-section pathology as the gold standard. This study was conducted in accordance with the principles outlined in the Declaration of Helsinki.

## 3.2 | EIS in clinical practice

The Impedimetric Tumor Detection Probe (ITDP) was inserted in the tumor and margins of the resected specimen under the supervision of a pathologist, and Z1 kHz and IPS were calculated and then compared with the gold standard. Applying ITDS as a complementary procedure confirmed the malignant nature of the tumor. Also, the ITDS on the right orbital bone margin was matched with the frozen and later permanent pathology reports. The point of our study is that the use of real-time intraoperative impedance-based tumor detection provided a correct observation about the pathological state of the suspicious resected borders, which was confirmed by frozen pathology and ultimately confirmed by permanent pathology.

In such cases, ex vivo real-time impedance-based tumor detection could be a helpful complementary procedure in the surgeon's estimation.

Many previously released reports reveal that EIS can alter clinical management and improve accuracy.[12–14] In this regard, Svoboda et al. assessed the impact of EIS results on clinicians' diagnostic accuracy and biopsy decisions. The results showed that the EIS score could lead to a change in the decision to biopsy in 25% of cases, improving diagnostic accuracy and resulting in fewer biopsies of benign lesions and more biopsies of melanomas. Also, including the EIS score, respondents' mean sensitivity and specificity for ruling out melanoma increased.[15] In another study, Vasudeva et al. demonstrated that EIS as an adjunct to colposcopy led to better detection rates in cervical intraepithelial neoplasms and elevated the sensitivity and specificity substantially.[16] Our previous study demonstrated that electrical impedance analysis of samples exhibits high sensitivity and specificity, thereby improving the in vivo diagnostic accuracy of metastatic lymph nodes during biopsy and surgery.[14] Hence, impedance detection could be applied in the real-time pathological evaluation of ACC cases to choose the correct treatment roadmap. Further studies are needed to justify the precision and applicability of ITDS for malignant orbital tumors.

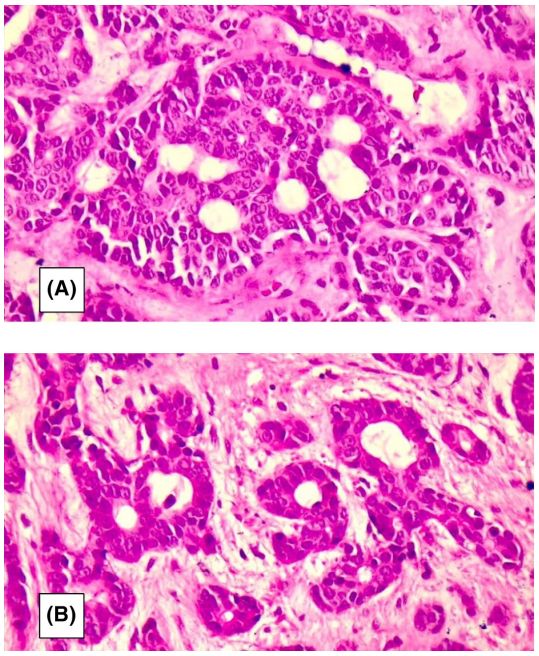


FIGURE 2 (A) Histopathology, H&E (x400), of the right orbit showing an epithelial neoplasm with a cribriform pattern, (B) Histopathology, H&E (x400), of the right orbit showing an epithelial neoplasm with a tubular pattern.

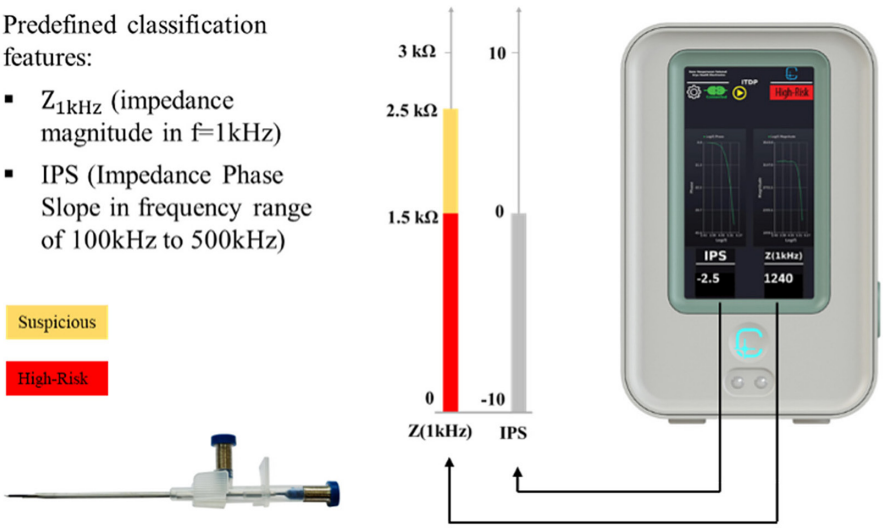


FIGURE 3 ITDS system, configuration, and calibration.

## 4 | CONCLUSION

When assessing orbital tumors, one must keep a high index of suspicion for ACC due to the aggressive character of this tumor and its propensity for recurrence, cerebral dissemination, and late distant metastasis. Tumor detection using EIS may be a helpful and rapid complementary intraoperative diagnostic procedure to assist in delineating precise surgical margins in malignant orbital tumors. The impact of real-time ITDS provides a pre-estimation about the necessity of excising malignant tissues in ACC to help the surgeon perform less invasive surgery, especially in the absence of frozen-section equipment.

## AUTHOR CONTRIBUTIONS

**Mohammad Reza Fattahi:** Conceptualization; data curation; writing – review and editing. **Mohammadkian Zarafshani:** Writing – original draft; writing – review and editing. **Mohammad Abdolahad:** Methodology; software; writing – review and editing. **Amirmohsen Jalaeefar:** Conceptualization; supervision; writing – review and editing. **Reihane Mahdavi:** Formal analysis; writing – review and editing. **Narges Yousefpour:** Formal analysis; writing – review and editing. **Hana Saffar:** Data curation; writing – review and editing. **Seyed Mohamad Sadegh Mousavi-Kiasary:** Formal analysis; writing – review and editing. **Farzad Pakdel:** Project administration; supervision; writing – review and editing.

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None.

## CONFLICT OF INTEREST STATEMENT

All authors declare that they have no conflicts of interest.

## DATA AVAILABILITY STATEMENT

None.

## CONSENT STATEMENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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