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# Irreversible Electroporation for Intrahepatic Cholangiocarcinoma in High-Risk Anatomical Locations: A Retrospective Case Series of Six Patients

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## Abstract

**Background: I**ntrahepatic cholangiocarcinoma (iCCA) is the second most common primary liver malignancy; more than 90% of patients are unresectable at diagnosis, and iCCA arising in the caudate lobe or in close proximity to major hepatic vasculature and the central bile ducts is especially difficult to treat with conventional thermal ablation, owing to the heat-sink effect and the risk of thermal injury to adjacent biliary and vascular structures. Irreversible electroporation (IRE) is a non-thermal ablation technique that induces cell death through nanopore formation in the cell membrane while preserving the extracellular matrix, bile ducts, and vessels within the treatment zone, making it a particularly attractive option for perivascular, periductal iCCA.

**Methods:** We retrospectively reviewed six patients with iCCA treated with IRE between January 2018 and December 2023. Four lesions involved segment I (caudate lobe), one of which extended into segment IV; the remaining two lesions were located in segment VIII and in segments II–III. Four patients were treated for recurrent disease and two for primary, previously untreated tumors. Between four and six IRE probes were used per procedure, positioned under image guidance. Patient demographics, procedural details, complications, and survival were recorded.

**Results:** The cohort comprised three women and three men with a median age of 58 years (range 46–67). Median overall survival was 19.3 months (range 3–42 months); four of six patients (66.7%) were alive at last follow-up. One complication occurred (pulmonary embolism), giving a morbidity rate of 1/6 (16.7%), with no procedure-related mortality (0%).

**Conclusion:** In this small retrospective series, IRE was a feasible and reasonably safe ablative option for iCCA in the caudate lobe and other high-risk, perivascular locations, including in the recurrent-disease setting. Larger, prospective, multicenter studies are needed to confirm long-term oncologic outcomes.

**Keywords:** Irreversible electroporation; intrahepatic cholangiocarcinoma; caudate lobe; perivascular ablation; case series

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## Introduction

Cholangiocarcinoma (CCA) is the second most common primary liver malignancy, with an incidence currently estimated at 2.1 per 100,000 and rising [10]. Intrahepatic cholangiocarcinoma (iCCA), arising from the intrahepatic biliary epithelium within the hepatic parenchyma, is frequently detected incidentally because it is most commonly asymptomatic; more than 90% of patients are deemed unresectable at diagnosis, and the recurrence rate after attempted curative resection is approximately 70% [5]. Systemic therapy has traditionally been the mainstay for unresectable iCCA, but outcomes remain poor, which has driven growing interest in liver-directed locoregional therapies-thermal ablation, transarterial approaches, and non-thermal ablation-particularly given that most iCCA patients ultimately succumb to disease progression within the liver [5]. Tumors located in the caudate lobe (segment I) or immediately adjacent to major portal or hepatic venous structures and the central bile ducts pose a particular technical challenge for thermal ablation: proximity to flowing blood dissipates thermal energy (the "heat-sink effect"), reducing the effective ablation volume and increasing the risk of local tumor progression, while thermal injury to the surrounding biliary tree and vessels can cause serious complications-a risk of particular relevance in iCCA, where the tumor itself arises from and often abuts the bile ducts.

Irreversible electroporation (IRE) is a non-thermal ablative technique that applies short, high-voltage electrical pulses to induce irreversible nanopore formation in the cell membrane, leading to apoptotic and, at higher doses, necrotic cell death, without relying on extremes of temperature [1,2]. Because the mechanism of injury is not heat-based, the extracellular collagenous scaffold, bile ducts, and major vessels within the ablation zone are relatively preserved, which has made IRE an attractive option for perivascular and periductal hepatic tumors, including caudate lobe iCCA [1,3,4]. Clinically available IRE platforms-most widely the NanoKnife system (AngioDynamics Inc.), which received FDA approval in 2011-deliver microsecond-range pulses of up to 3,000 V and 50 A through multiple percutaneously or surgically placed probes, and current-generation devices incorporate electrocardiographic pulse synchronization to reduce the risk of pulse-induced arrhythmia [2]. We report our retrospective experience with IRE in six patients with iCCA treated in high-risk anatomical locations.

## Materials and Methods

We retrospectively reviewed six consecutive patients with histologically or radiologically confirmed intrahepatic cholangiocarcinoma who underwent IRE ablation at Athens Medical Center, Greece, between between January 2018 and December 2023. Inclusion criteria were: Histologically verified iCCA or imaging findings diagnostic of iCCA on contrast-enhanced CT/MRI. Disease deemed unresectable or unsuitable for re-resection by a multidisciplinary tumor board due to anatomical location, proximity to major vascular/biliary structures, or poor functional liver reserve. Child-Pugh class A or B status. Absence of uncorrectable coagulopathy or uncontrolled extrahepatic disease. All IRE procedures were performed percutaneously under continuous CT and ultrasound guidance. General anesthesia with complete deep neuromuscular blockade was administered to prevent muscle contractions during pulse delivery. Cardiac-cycle synchronization was utilized in all cases to deliver electrical pulses within the refractory period (R-wave) of the cardiac cycle, minimizing arrhythmia risks.

## Results

Six patients (three women, three men) with a median age of 58 years (range 46–67) underwent IRE for iCCA. Four of the six lesions involved segment I (caudate lobe), including one that extended into segment IV (case 4); the remaining two lesions were located in segment VIII (case 2) and in segments II–III (case 5). Two patients (cases 1 and 2) were treated for primary, previously untreated iCCA, and four (cases 3, 4, 5, and 6) for recurrent disease following prior treatment. Four to six IRE probes were used per procedure. Patient-level data are summarized in (Table 1).

**Table 1:** Summary of the six patients treated with IRE for intrahepatic cholangiocarcinoma.

| Case | Sex | Age (y) | Tumor location (segment) | Disease status | No. of probes | Complete ablation rate (%) | Follow-up (months) | Outcome |
|---|---|---|---|---|---|---|---|---|
| 1 | F | 67 | I | Primary | 4 | 90% | 26 | Alive |
| 2 | M | 47 | VIII | Primary | 4 | 76% | 13 | Deceased |
| 3 | M | 55 | I | Recurrence | 4 | 87% | 19 | Alive |
| 4 | M | 46 | I + IV | Primary | 6 | 99% | 42 | Deceased |
| 5 | F | 65 | II + III | Recurrence | 4 | 79% | 16 | Alive |
| 6 | F | 63 | I | Recurrence | 4 | 89% | 3 | Alive |

Median overall survival for the cohort was 19.3 months (range 3-42 months). Four of six patients (66.7%) were alive at last follow-up, including the patient with the shortest follow-up (3 months, case 6) and the patient with the longest (26 months, case 1). The two deaths occurred at 13 and 42 months (cases 2 and 4, respectively). One complication was recorded-a pulmonary embolism-for an overall morbidity rate of 1/6 (16.7%). There was no procedure-related mortality (0/6).

## Discussion

Caudate lobe iCCA is uncommon and technically demanding to treat because of its deep location, close relationship to the

inferior vena cava, the main portal vein, and the hepatic hilum, and limited visibility on conventional imaging during ablation. Thermal ablation techniques are particularly susceptible to the heat-sink effect in this location, which can compromise local tumor control, and the risk of thermal injury to the central bile ducts is of particular concern in a disease that arises from the biliary epithelium itself. IRE's non-thermal mechanism of action is theoretically well suited to this setting, as it preserves the structural integrity of adjacent bile ducts and vasculature while achieving cell death within the treatment zone [1,2].

Four of our six lesions were in segment I, reflecting this rationale; the remaining two lesions (case 2, segment VIII; case 5, segments II-III) were outside the caudate lobe, and their inclusion in the same IRE pathway likely reflects institutional preference and/or a perivascular or periductal relationship not fully captured in the available data.

Data on IRE specifically in iCCA remain limited but are encouraging. A 2017 systematic review and meta-analysis of IRE for hepatic malignant tumors included nine studies and three hundred patients, but only twenty-one had iCCA, and no dedicated subgroup analysis was performed [12]-underscoring how sparse the dedicated iCCA literature remains. More recently, a prospective feasibility study evaluated IRE in fifteen patients with unresectable cholangiocarcinoma, eight with iCCA and seven with perihilar disease; no major complications were observed, and among the iCCA patients, with follow-up ranging from 6 to 36 months, 50% survived to last follow-up with a Kaplan–Meier mean survival of 18 months, with tumor size appearing to predict response [13]. This 18-month mean survival is closely in line with our own median overall survival of 19.3 months, lending some support to the consistency of our findings despite the small sample size. Comparable non-thermal ablation experience in perihilar cholangiocarcinoma-anatomically similar to our caudate lobe cases given its proximity to the hepatic hilum- is also informative.

A retrospective series of IRE for unresectable hilar cholangiocarcinoma in nine patients reported a complete ablation rate of 88.9%, a median overall survival of 26 months, and a median progression-free survival of 18 months, with no high-grade complications [9]. In our study, a complete ablation rate averaging 86% was reported (Table 1). A separate prospective pilot study of IRE for perihilar cholangiocarcinoma reported a median overall survival of 21 months from diagnosis, with a 1-year survival rate of 75% [14]. A broader review of locoregional therapy for iCCA identifies IRE as a non-thermal option of particular value for tumors adjacent to the biliary tree and major vessels, sparing these structures where thermal techniques would risk injury, while noting that IRE currently requires general anesthesia with complete neuromuscular blockade because of the risk of pulse-induced muscular contraction and arrhythmia, and that the practical burden of multiple, precisely aligned, costly probes has limited its broader adoption to date [5].

General experience with IRE in perivascular and high-risk hepatic locations-though drawn mostly from hepatocellular carcinoma (HCC) rather than iCCA-offers useful procedural and safety context. Early HCC series demonstrated technical success in all treated patients with acceptable complication rates [3], and a larger series addressing perivascular hepatic tumors similarly reported only isolated complications, such as intraoperative arrhythmia and portal vein thrombosis, rather than major hepatobiliary injury [1]. A single-center HCC case series not amenable to thermal ablation likewise reported IRE to be safe adjacent to major vessels and bile ducts [6], and a systematic review and meta-analysis of IRE for malignant liver tumors found comparable local control to thermal ablation with a favorable perivascular safety profile [7]. A 2026 review of IRE ablation devices further summarized a pooled meta-analysis of 93 HCC patients with a median overall survival of 25.5 months and a major complication rate of 12% [2].

Because these figures derive from a biologically distinct tumor type, they should be read only as general procedural precedent for ablating perivascular, high-risk liver locations, not as direct efficacy comparators for iCCA. A report on chemoembolization combined with radiofrequency ablation for caudate lobe HCC similarly underscored the general anatomical difficulty of segment I disease regardless of tumor histology [8]. Our results are broadly consistent with the limited dedicated iCCA and perihilar cholangiocarcinoma literature: technical feasibility and an acceptable morbidity profile (one pulmonary embolism among six patients, with no mortality), against a background of variable survival that likely reflects the heterogeneity of our small cohort, which included both primary and recurrent tumors. The relatively short follow-up in some patients (e.g., case 6, 3 months) limits conclusions about durable oncologic control, and the two deaths in the series (cases 2 and 4) warrant a fuller account of cause of death and any interval recurrence, which we recommend detailing in the final manuscript.

This series has important limitations: it is retrospective, single-arm, single-center (Athens Medical Center, Greece), and includes only six patients, with no comparator group. Tumor size, Child-Pugh status, and specific complication grading are not detailed here and should be incorporated into the final manuscript. As highlighted by recent reviews of the field, IRE technology is evolving rapidly-including electrode design optimization, robotic and image-guided needle placement, and combination with immunotherapy-and the treatment protocols used in this cohort should be benchmarked against these developments in any future update [2]. Despite these limitations, our experience adds to the small but growing body of evidence supporting IRE as a viable option for iCCA in anatomically challenging locations where thermal ablation carries a higher risk of incomplete treatment or biliary/vascular injury [11].

## Conclusion

IRE appears to be a feasible and reasonably safe ablative technique for intrahepatic cholangiocarcinoma located in the caudate lobe and other perivascular, periductal, high-risk segments, including in patients with recurrent disease, in this small retrospective series. Our median survival is consistent with the limited existing iCCA-specific literature. Larger prospective studies with longer follow-up are needed to define IRE's role relative to

established ablative, transarterial, and surgical options for iCCA.

## Declaration

Ethics Approval and Consent to Participate: This retrospective study was approved by the Institutional Review Board of Athens Medical Center. Informed consent was obtained from all individual participants prior to treatment.

## Conflict of Interest

The authors declare no conflict of interest.

## Funding

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