Irreversible electroporation for treatment of colorectal cancer in a porcine model

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Electroporation (EP) is a novel, highly selective, nonthermal modality for tissue ablation.[1] Reversible EP occurs when an electrical field is applied to the target cell creating transmembrane potential differences that result in transient micropores in the cell membrane. Increased cell membrane permeability allows passage of poorly absorbable substances such as chemotherapeutic agents or toxic cations such as calcium into cells. Irreversible EP (IRE), also known as pulsed field ablation, can be generated by adjusting the electrical parameters, particularly increasing electrical voltage and treatment duration that prevents closure of micropores in cell membranes, leading to irreversible cell death.[2] Initial studies have shown promising results of IRE as monotherapy in pancreatic and prostate cancers.[3,4] We performed a feasibility study using 5 genetically modified animals to describe the use and safety of IRE using a novel EP device (EndoVE; Mirai Medical, Galway, Republic of Ireland). The study was approved by the Institutional Animal Care and Use Committee.

Preclinical application of endoscopic IRE (Fig. 1) for colorectal cancer (CRC) requires a large animal model. Successful OncoPig models for hepatocellular carcinoma, sarcoma, and pancreatic cancer have been described.[5] Our porcine CRC model was a genetically modified pig with inducible transgenes ending for Kirsten rat sarcoma viral oncogene and tumor protein p53 driver mutation. The adenoviral vector activates the mutation, leading to cancer formation.[6] Each animal underwent submucosal viral vector (Sus Clinicals Inc, Cincinnati, Ohio, USA) injection for tumor induction in the colorectum, with tattoo placement for identification (Fig. 2). The dwell time from tumor induction to IRE was 2 weeks.

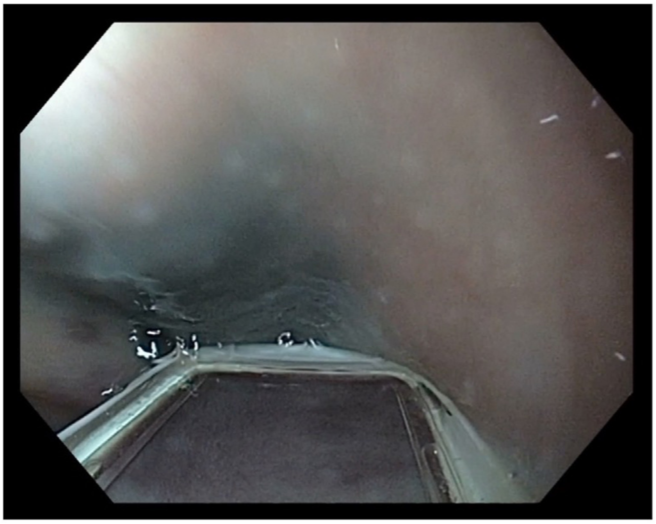

Figure 1. Endoscopic irreversible electroporation therapy.

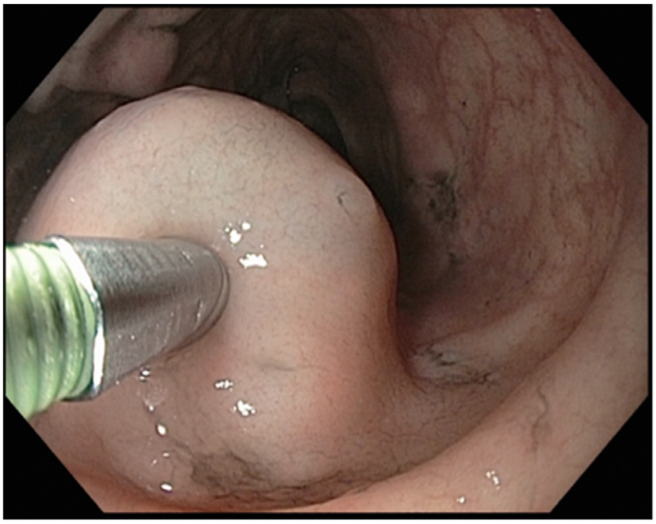

Figure 2. Tumor creation with injection of viral vector.

The EP device was mounted onto a standard pediatric colonoscope (Fig. 3). The EndoVE probe consists of a chamber

Abbreviations: CRC, colorectal cancer; EP, electroporation; IRE, irreversible electroporation; IQR, interquartile range.

2468-4481
https://doi.org/10.1016/j.vgie.2024.12.002

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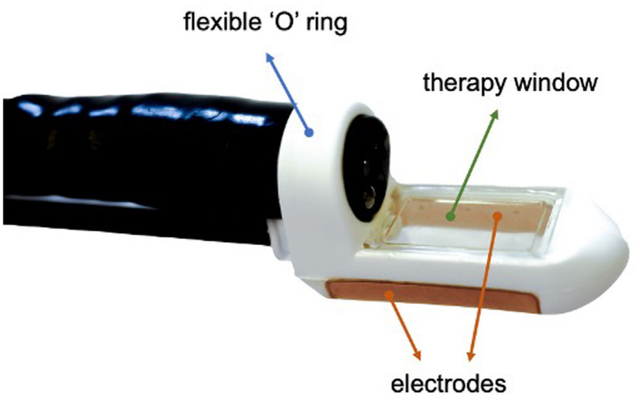

Figure 3. Irreversible electroporation device.

Figure 4. Irreversible electroporation generator.

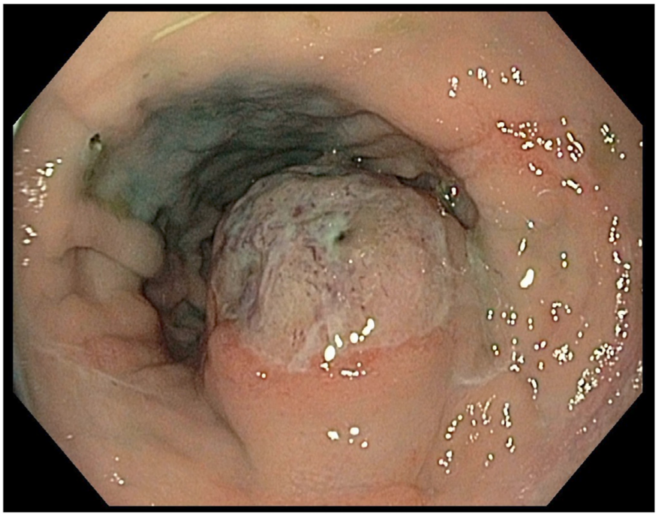

Figure 5. Tumor with extensive mucosal ulceration.

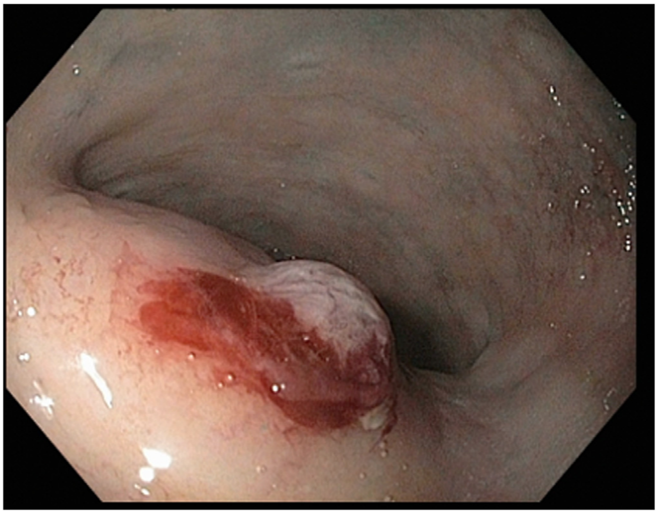

Figure 6. Tumor with focal mucosal ulceration.

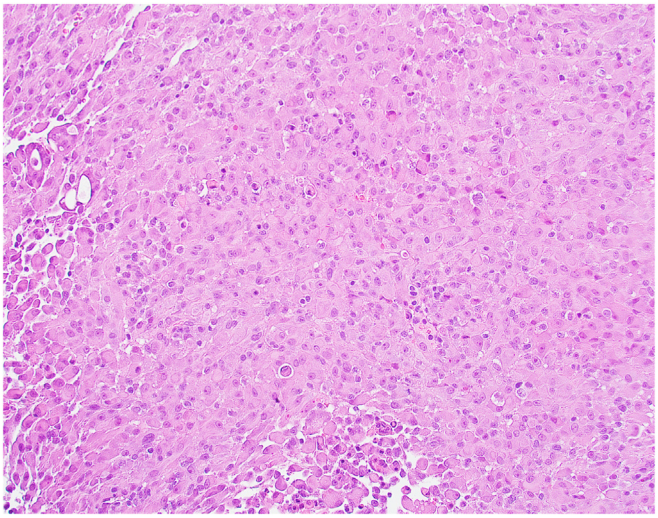

Figure 7. Poorly differentiated carcinoma on histopathology (H&E, 200× total magnification).

that uses a vacuum to draw target tissue into contact with the electrodes. The device was placed directly onto the tumor surface at the 6 o'clock position. The generator (ePORE; Mirai Medical) delivers a series of high-frequency electrical pulse bursts of biphasic waves with a frequency of 10 Hz and an electrical field intensity of 1 kV/cm (Fig. 4). The minimum ablation volume was 1.5 cm^3. After each ablation, the chamber was irrigated with distilled water to control the rising temperature and prevent thermal injury. The probe was then repositioned to treat residual areas (Video 1, available online at www.videogie.org). The EP device has a CE (Conformité Européenne) mark and is not currently FDA approved.

Ten tumors were successfully treated with good (4/10) or fair (6/10) contact with the EP probe. Good probe

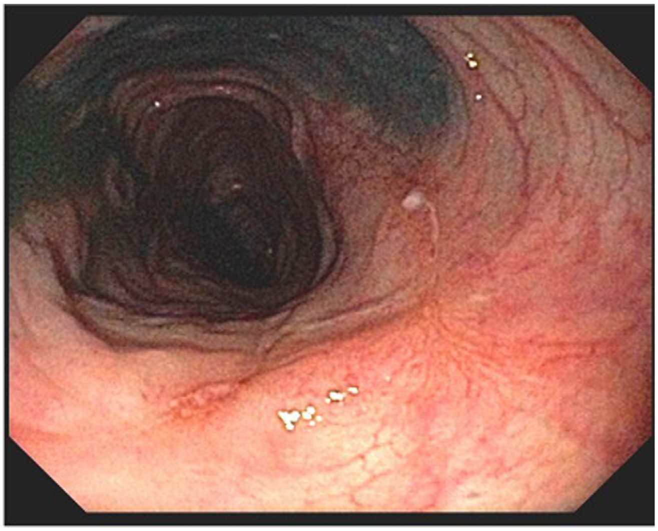

Figure 8. Scarring post-irreversible electroporation.

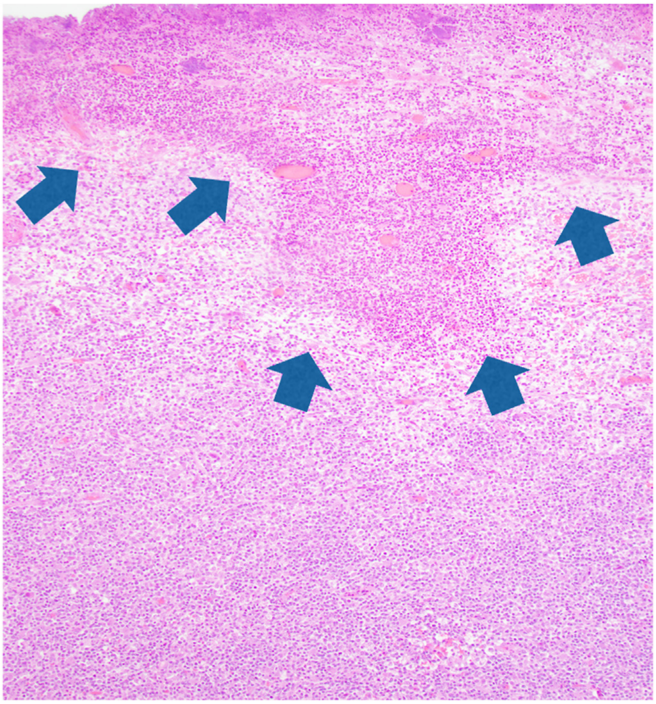

Figure 9. Necrosis (*arrows*) post-irreversible electroporation (H&E, 40× total magnification).

contact was defined as a contact area >90%, whereas fair probe contact was defined as a contact area >75% and <90%. The median tumor diameter at baseline was 4.75 cm (interquartile range [IQR], 4.0-5.0 cm). Tumors were predominantly subepithelial with 4 masses demonstrating extensive mucosal ulceration (Fig. 5) and 6 tumors with focal ulceration (Fig. 6). Histology confirmed poorly differentiated carcinoma (Fig. 7). Animals had an uneventful clinical course. There were no procedure-related adverse events. Animals were killed at 5 timepoints (5 days and 1, 2, 3, and 4 weeks after treatment). Repeat endoscopy was performed before necropsy and showed reduction in tumor size (10/10), ulceration (9/10), and scarring (1/10) at treatment sites (Fig. 8). The median tumor diameter at follow-up endoscopy was 2.5 cm (IQR, 0.5-3.5 cm). Necropsy showed no delayed adverse events. Histopathology demonstrated presumed IRE-related necrosis based on distribution of necrosis extending from the treated mucosal surface to a depth of 1 to 1.5 mm, inflammation, and fibrosis (Fig. 9 and Table 1).

TABLE 1. Histopathological findings

Time after irreversible electroporation	Histopathology
5 days	Tumor with superficial necrosis (1 mm depth), no fibrosis
1 week	Tumor with superficial ulceration and necrosis (1-1.5 mm depth), no fibrosis
2 weeks	Tumor with superficial ulcer, no fibrosis
3 weeks	Extensive chronic inflammation, no fibrosis
4 weeks	Chronic inflammation and fibrosis

Our study is limited by a small dataset, and although additional studies are needed, IRE technology appears to be a potentially safe and effective modality that may have a future role in CRC adjunct therapy and palliation.

DISCLOSURE

Dr Rajan has intellectual property relation with Medtronic and Ruhof; is a consultant for Olympus and Johnson & Johnson; and has undertaken research for Mirai Medical, FujiFilm, and CapsoVision. Dr Kamba is a consultant for Lpixel and FujiFilm; has received research grants from FujiFilm; and receives royalty income from Boston Scientific Japan. Dr AbiMansour receives royalty income from Ruhof. The other authors have no financial relationship(s) to disclose.

ACKNOWLEDGMENTS

This study was supported by Mirai Medical (Galway, Ireland) for study funding and providing EndoVE devices, and Sus Clinicals (Ohio) for providing OncoPigs and adenoviral vector.

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