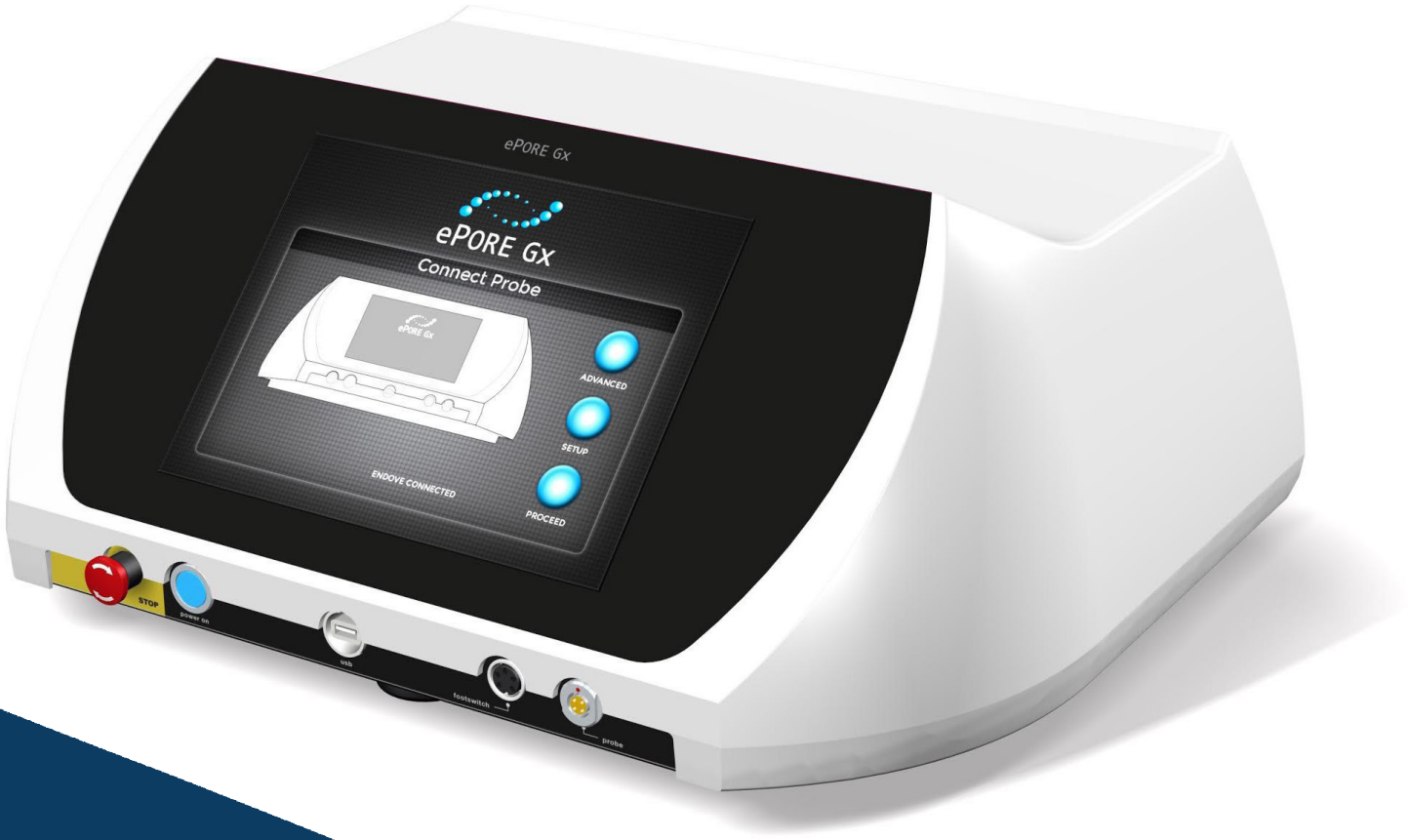
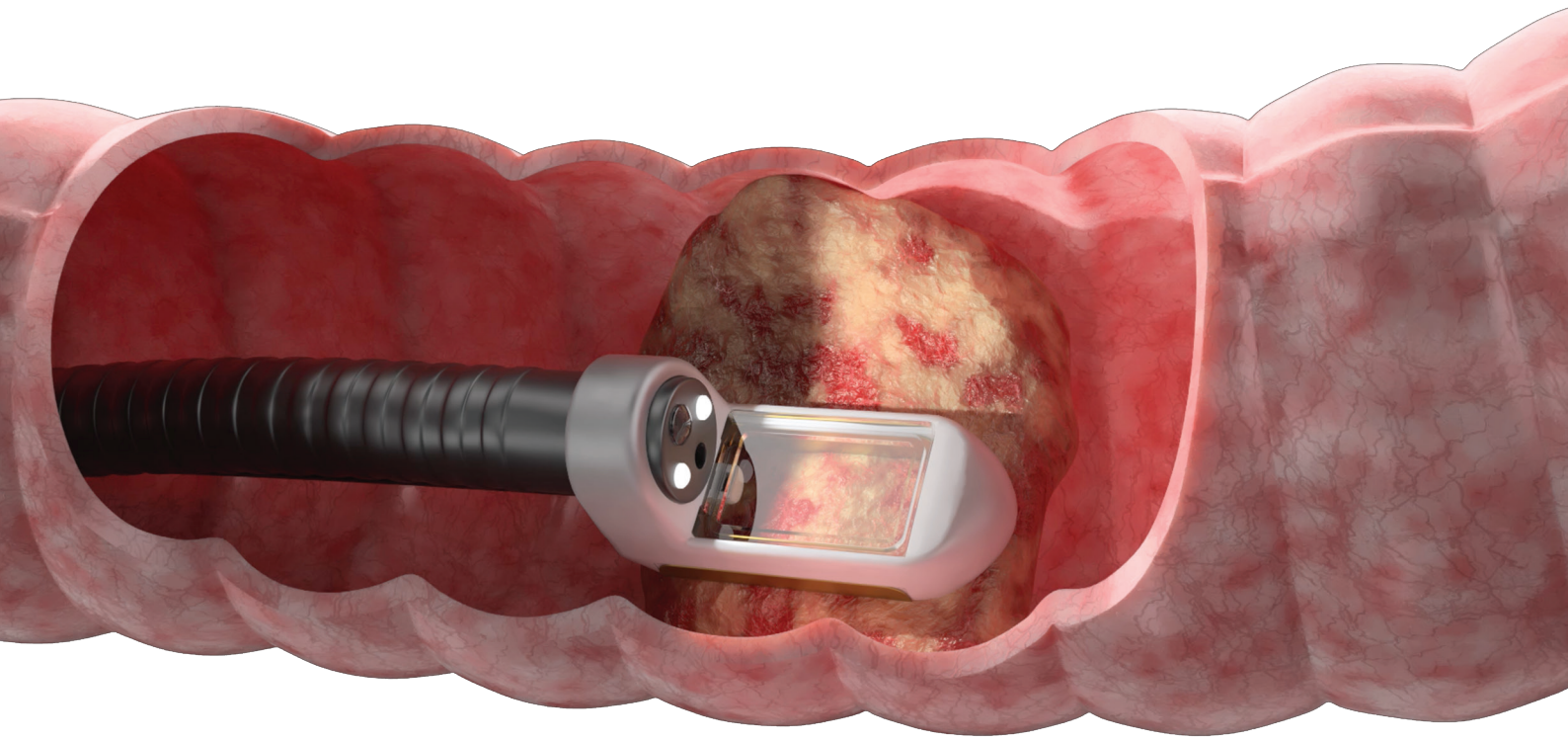



DUOMED

# ePORE & endoVE PRECISION

## INTERVENTIONAL ENDOSCOPY TREATMENT FOR GASTROINTESTINAL CANCER

IN PARTNERSHIP WITH MIRAI MEDICAL



## About Duomed UK

*Duomed UK is an innovative organisation , breaking new ground in the endoscopy healthcare environment. We are driven to provide outstanding customer service and product solutions. All our teams are united in the understanding that what we do every day, makes a difference to our customers and their patients.*

*We apply purpose driven products and solutions from around the globe, to help facilitate improved delivery of healthcare in the NHS and private sectors.*
*Duomed UK is a part of The Duomed Group, a dynamic organization with a well-established reputation. The Duomed Group are active in consultancy, sales, integration, training and technical support of medical technology and devices for hospitals and medical practices.*

## About Mirai Medical

Following over 15 years of research and development, Mirai Medical was formed from a team with over 50 combined years of experience in the field of cancer electroporation and medical device development.

Their extensive R&D work has put the patient experience at the front and centre of our treatment platform. We are excited to work with clinicians on the utilisation of this important precision tool for cancer treatment.

clinicians on the utilisation of this important precision tool for cancer treatment.

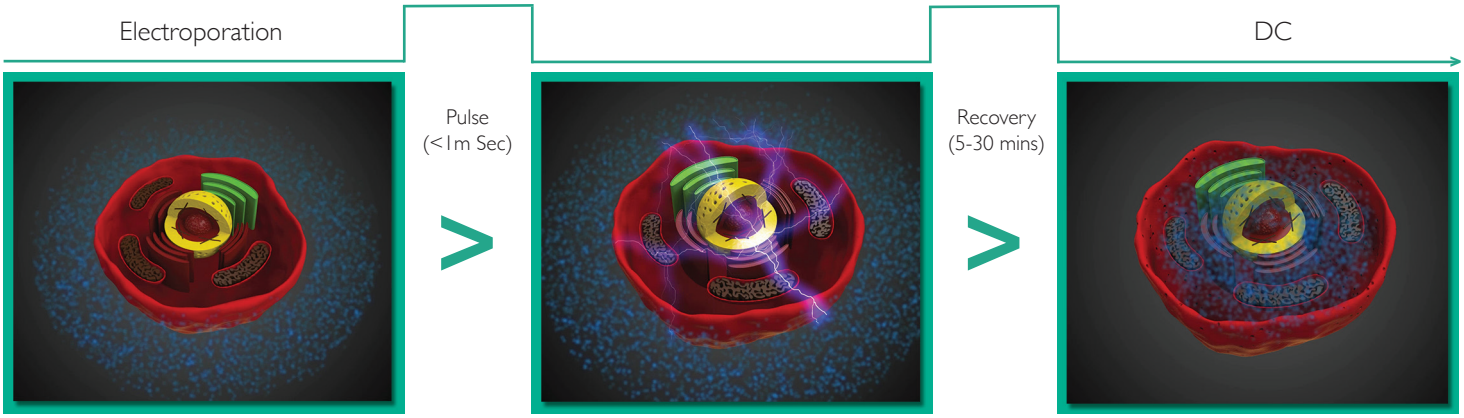
MIRAI MEDICAL has developed an endoscopic approach to target gastrointestinal cancers by utilizing an energy-based technology called electroporation. This treatment approach essentially causes tumour tissue to become extremely porous for several minutes allowing for greater absorption of specific chemotherapy drugs.

# How Does Electroporation Work?

**Electroporation with chemotherapy has been in clinical use for more than 15 years and in 2006 the European Standard Operating Procedure (ESOPE) which described the standard delivery of the procedure including chemotherapy dose.**

Of great benefit, due to the greater conductivity of tumour tissue, the surrounding healthy tissue structures are not damaged in the process.

The effectiveness of electroporation in tumour ablation clinically has been reported by a growing number of clinicians in the US and Europe with excellent quality of life and tumour reduction reported for both cutaneous and intraluminal applications.




Cell Membrane Before Pulse

Cell Membrane During Pulse

Cell Membrane After Pulse
(Cell Returned to Original State)

# Role of ePORE Therapy in Gastrointestinal Cancers

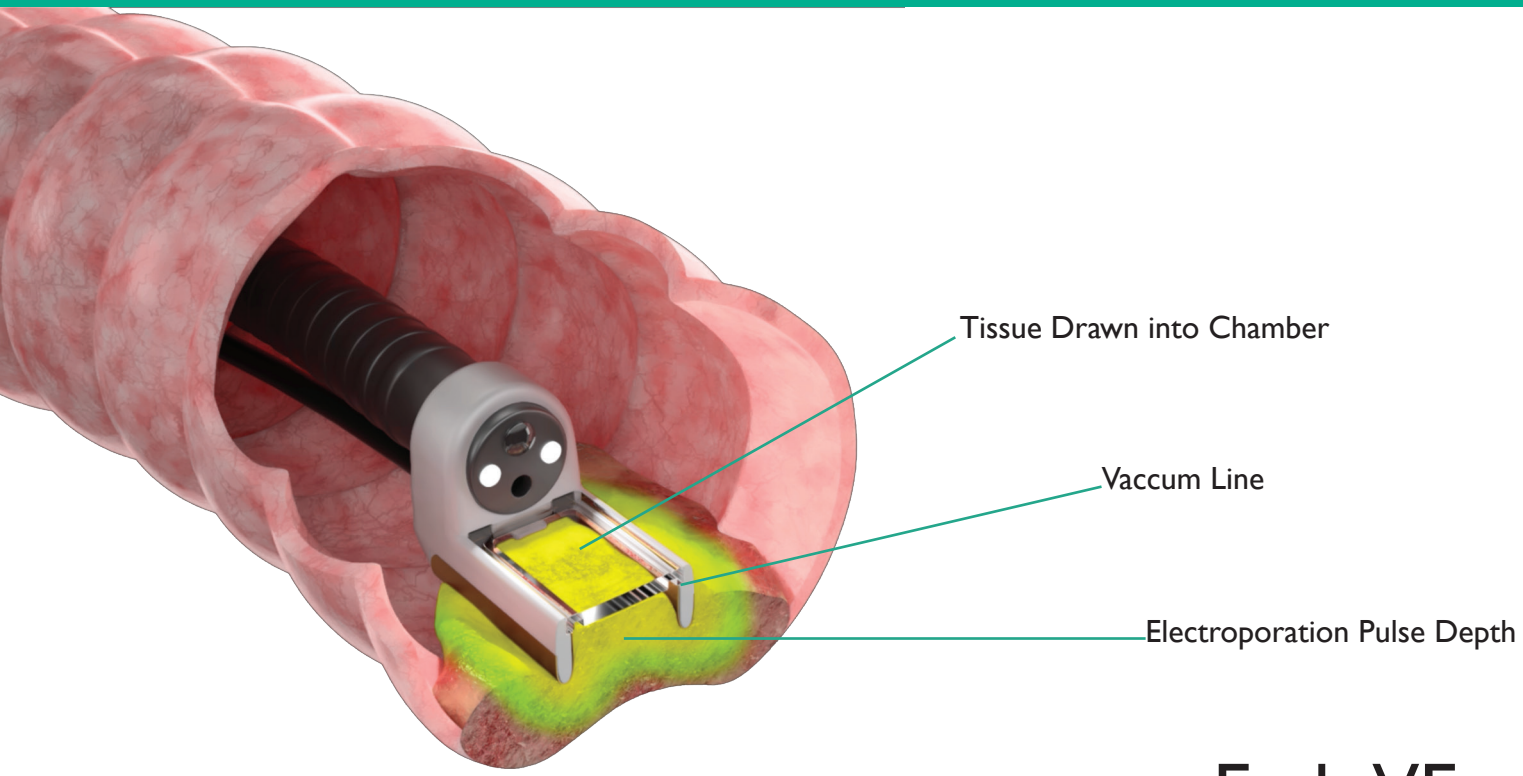
The role of pulsed electrical fields or electroporation, generated by the ePORE which increases the cell membrane porosity of gastrointestinal cancers has been extensively researched and published on. A specially designed device, the EndoVE, has been developed to enable the safe and effective application of pulses to GI cancers with a number of successful clinical studies now completed.

Currently the indications for use with ePORE therapy in the GI cancer setting is for palliation of symptoms (bleeding cessation, pain relief, decreasing tumour volume).

A number of studies are currently ongoing to explore a wider application to include earlier stage disease and to explore the intratumoral immune response generated after ePORE therapy.

Our EndoVE probe attaches to a standard gastroscope or colonoscope and delivers pulsed electrical fields generated by the ePORE to the tumour cells, allowing an injected chemotherapeutic drug to passively diffuse far more effectively into the cancer cells and kill them.

The vacuum feature in the endoscopic electrode assists in drawing tumour tissue into direct contact with the electrodes contained within the EndoVE device. There is minimal discomfort associated with the procedure, and reduction in the size of the tumour can be achieved in just one session. Additionally, treatment with EndoVE has been shown to aid in achieving a reduction in bleeding, which can be a symptom of many GI cancers. Overall, the EndoVE has been shown to decrease symptoms and improve patients' quality of life.




# EndoVE

The procedure is similar to a standard endoscopy and is performed under sedation. A single low dose of the chemotherapy drug (bleomycin or cisplatin) is provided via intravenous or intratumoural injection. Calcium has also now been demonstrated to be as effective when injected intratumourally and can be used to replace the chemotherapy drug.

The EndoVE system delivers electroporation pulses directly to the tumour tissue via the ePORE generator with the process repeated several times until the entire tumour surface area and surrounding margins have been treated. Typically the total procedure takes 20 minutes. Once recovered, the patient will be monitored for several hours before being released on the same day.

# Advantages of EndoVE & ePORE Therapy

Demonstrated to be safe and effective with Minimal hospital stay and resources required.

Precision delivery of non-thermal ablation which targets tumour tissue whilst preserving surrounding healthy tissue structures.

Simple standard connection for endoscopes between 9mm and 10mm.

Connects to a vacuum which draws the tumour tissue into the chamber this can be viewed via the window at the head of the electrode.

Highly effective at local tumour control and non-toxic

Excellent patient quality of life benefits

Tumour specific treatment with healthy tissue preservation

Reduces symptoms such as bleeding and pain associated with GI cancers

Repeatable procedure leaving standard options available

# ePORE Therapy Procedure For GI Cancers

The treatment is delivered with the patient receiving the appropriate endoscopy sedation.

The chemotherapeutic drug or calcium solution being combined with the electroporation treatment is administered.

The patient is treated under normal endoscopy/colonoscopy sedation. The EndoVE probe, is attached to the endoscope and positioned in close proximity to the tumour tissue by the clinician. A vacuum is utilised by the EndoVE to draw the tumour tissue into contact with electrodes and the pulsed electrical fields are then delivered in a matter of seconds by the ePORE.

Tumour tissue within the vicinity of the pulsed electrical fields become significantly more porous allowing the uptake of drug far more efficiently and inducing tumour cell death.

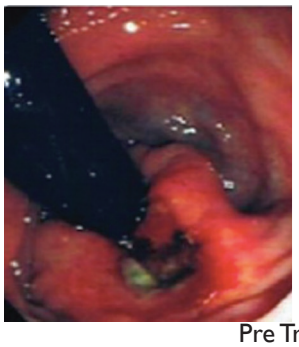
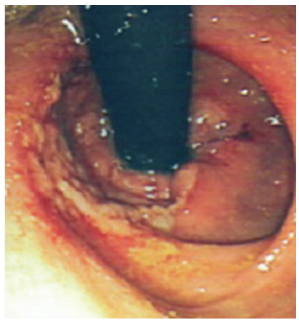
Healthy tissue in the margins remains largely unaffected by the procedure due to conductivity differences between healthy and tumour tissue in addition to the greater ability for healthy cells to recover quickly from the stress of the pulsed electrical fields.

# Clinical Experience

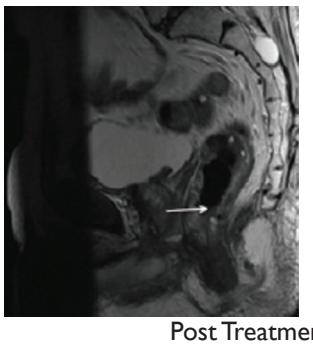
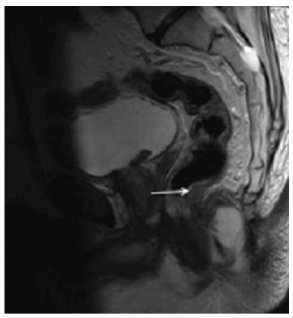
The EndoVE system has been assessed in clinical trials for patients with inoperable colorectal and oesophageal cancer. The clinical evidence to date with electroporation has demonstrated its excellent efficacy in tumour treatment even in cases where tumours were previously unresponsive to chemotherapy or radiotherapy.

No evidence of perforation or other adverse events have been observed to date. The EndoVE device has demonstrated excellent utility in resolving large circumferential tumours, which typically require two endoscopic sessions for treatment. Future clinical trials are planned to establish use in the earlier stages of disease, in combination with nonchemotherapeutic agents e.g. Calcium. In addition Electroporation has demonstrated synergy with immunotherapy.

## Colo Rectal - T3N2 Rectal Cancer

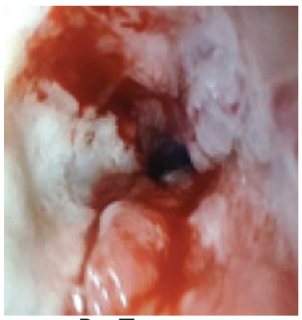



Pre Treatment

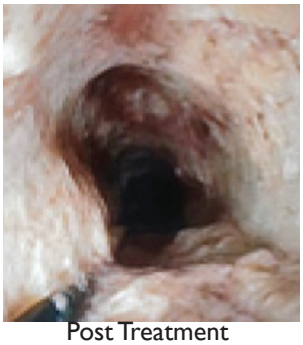



Post Treatment (3 Months)

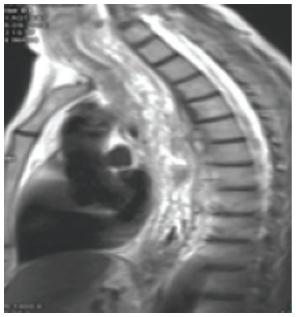
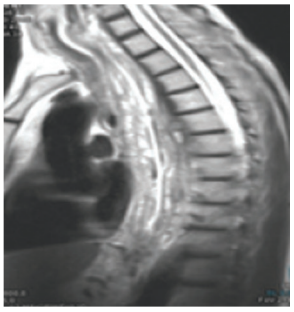
## Oesophageal Cancer - T3 Oesophageal Cancer



Pre Treatment



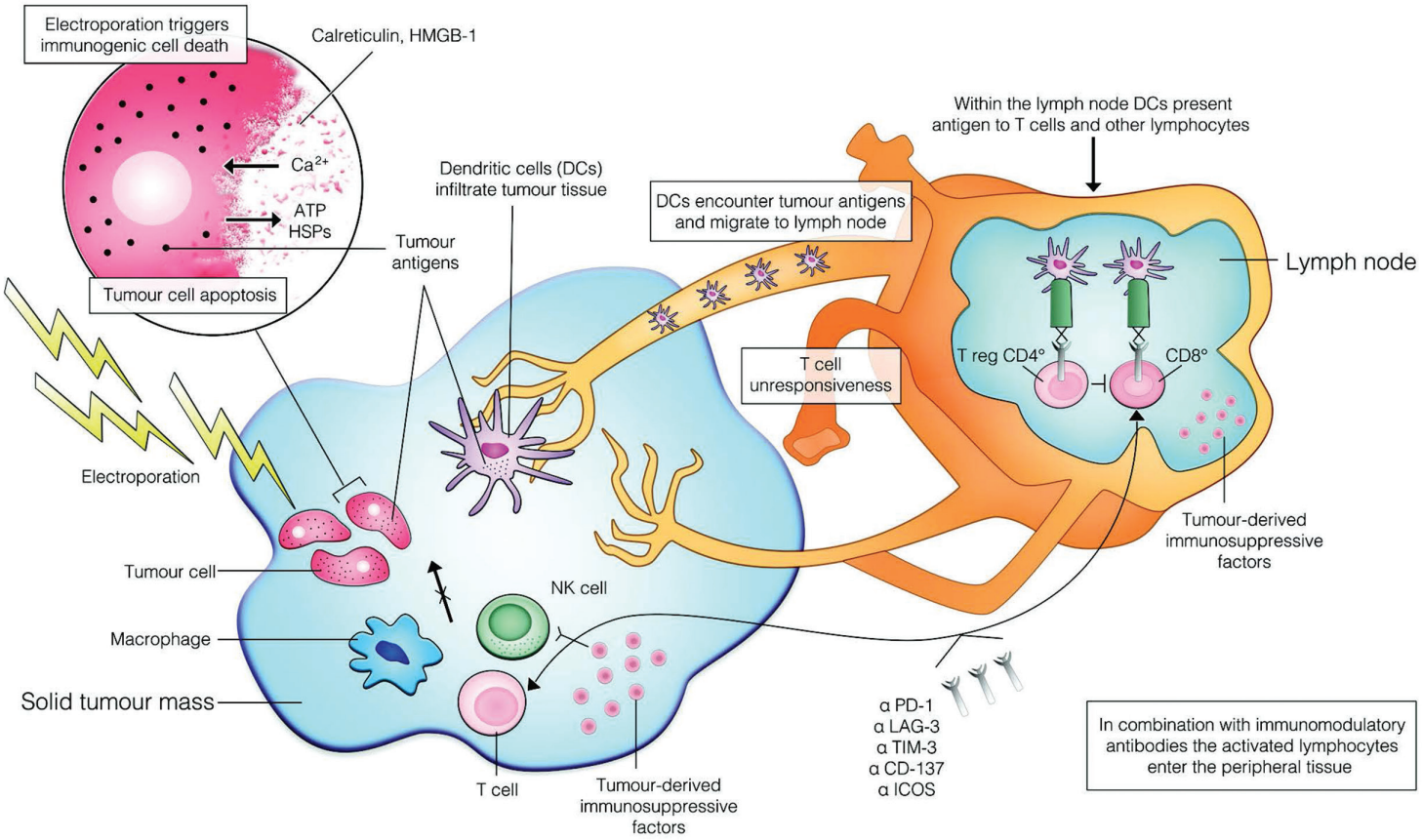
Post Treatment
(4 Weeks)

Post Treatment

# Interventional Endoscopy Treatment for Gastrointestinal Cancer

**Mirai Medical is an exciting next-generation cancer treatment company bringing a ground-breaking cancer solution to patients and clinicians.**





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# FAQ's

**Q: How does an R wave detector (heart sync) impact the treatment of upper GI or gastric cancer?**
Upper GI cases (oesophageal and gastric) utilise an ECG monitor and R wave trigger to ensure safe delivery of the pulsed electrical fields and minimise any risk of cardiac arrhythmia. An ECG R wave trigger can be directly connected to the ePORE in such cases. Please refer to the ePORE user manual for more detailed information.

**Q: What type of cancers can be treated?**
ePORE therapy for GI cancers can be used for the treatment of solid tumours of the GI tract including oesophageal, gastric and colorectal cancer.

**Q: Can ePore therapy be repeated?**
ePORE therapy can be repeated as necessary, to improve the response to the treatment as felt appropriate by the clinical team managing the case.

**Q: Can the patient be treated under local anaesthetic?**
Yes, ePORE therapy delivers high frequency pulsed electrical fields which can be administered to GI cancers directly with the EndoVE device. A procedure may be carried out under light sedation or under certain circumstances may require general anaesthesia and this will be pre-determined by the operating clinical team.

**Q: Can ePORE therapy treat patients within a day?**
Patients are usually treated as a day case; however, this must be assessed on a patient-by-patient basis and in some cases, it may be more appropriate to keep the patient under surveillance for the night after the operation.

**Q: Are there any side effects?**
Some patients may experience a mild fever following the treatment, but pain-relieving medication can be prescribed to relieve this. Serious side effects are extremely rare. In very few cases, patients may have an allergic reaction to the chemotherapy drug or may experience shortness of breath.

**Q: Is it purely palliative?**
This is determined by the stage of the disease and how far advanced it is at the time of treatment. Typically, early-stage disease is managed with local surgery with more advanced disease treated using a combination of surgery, chemotherapy and radiotherapy. ePORE therapy delivered with EndoVE is currently utilised for later stage disease in patients considered unsuitable for surgery with the goal of controlling symptoms and improving patient's overall quality of life. Research and clinical studies in managing GI cancers with EndoVE in combination with calcium are ongoing in earlier stage disease.

**Q: How does ePORE therapy reduce bleeding in GI cancers?**
ePORE therapy aids in stopping or reducing bleeding caused by GI cancers by immediately inducing vasoconstriction of the capillaries supplying blood flow to the tumour. Additionally, ePORE therapy results in long-term disruption of the cytoskeletal structure of the tumour cells, and also causes the barrier function of the microvascular endothelium to be compromised. Tumour cells are consequently exposed to a lack of oxygen and nutrients due to the disruption in blood flow to the tumour and facilitates inducing their death (Jarm et al., 2014).

**Q: Can you use ePORE therapy with other treatments?**
As ePORE therapy is a localised non-toxic treatment, it can be used in conjunction with other treatment options.

**Q: Can ePORE therapy be used if the patient has a pacemaker?**
If a patient has a pacemaker, then treatment should not be delivered in areas that are in close proximity to the pacemaker. Please refer to the ePORE user manual for more information.

**Q: What doses of Bleomycin must be used, is it safe?**
Very low concentrations of bleomycin are used and maintain their effectiveness due to the increased porosity of the tumour cells, thereby allowing maximum absorption of a low dose chemotherapeutic drug. If bleomycin is injected intravenously, the dose provided is 15,000 IU/m2. If injected intratumorally, it is delivered at a concentration of 1000 IU/ml with the total dosage determined by the volume of the tumour (Mir et al., 2006). Very few side effects associated with the use of bleomycin in combination with pulsed electrical fields have been observed as the doses used are significantly lower than the standard doses deployed during conventional chemotherapy treatment.

**Q: Which cancers are more responsive to ePORE therapy?**
The published evidence demonstrates that pulsed electrical fields, tissue electroporation, is effective in a wide range of solid tumour histology subtypes. To date in fact, no solid tumour has been discovered to be resistant to pulsed electrical fields rendering their cell membrane porous. Typically, bleomycin when delivered alone is used in only a small number of cancer types however when administered in combination with pulsed electrical fields its effectiveness is greatly expanded. Bleomycin works by binding with DNA and breaking its structure which forces the cell into a cell death pathway. Very few molecules of bleomycin are required to trigger cell death however normally its ability to enter a cell is limited due to the large size of the bleomycin molecule and its inability to cross the cell membrane. ePORE therapy overcomes this barrier and enables highly effective localised tumour cell death without toxicity to healthy tissue structures.

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