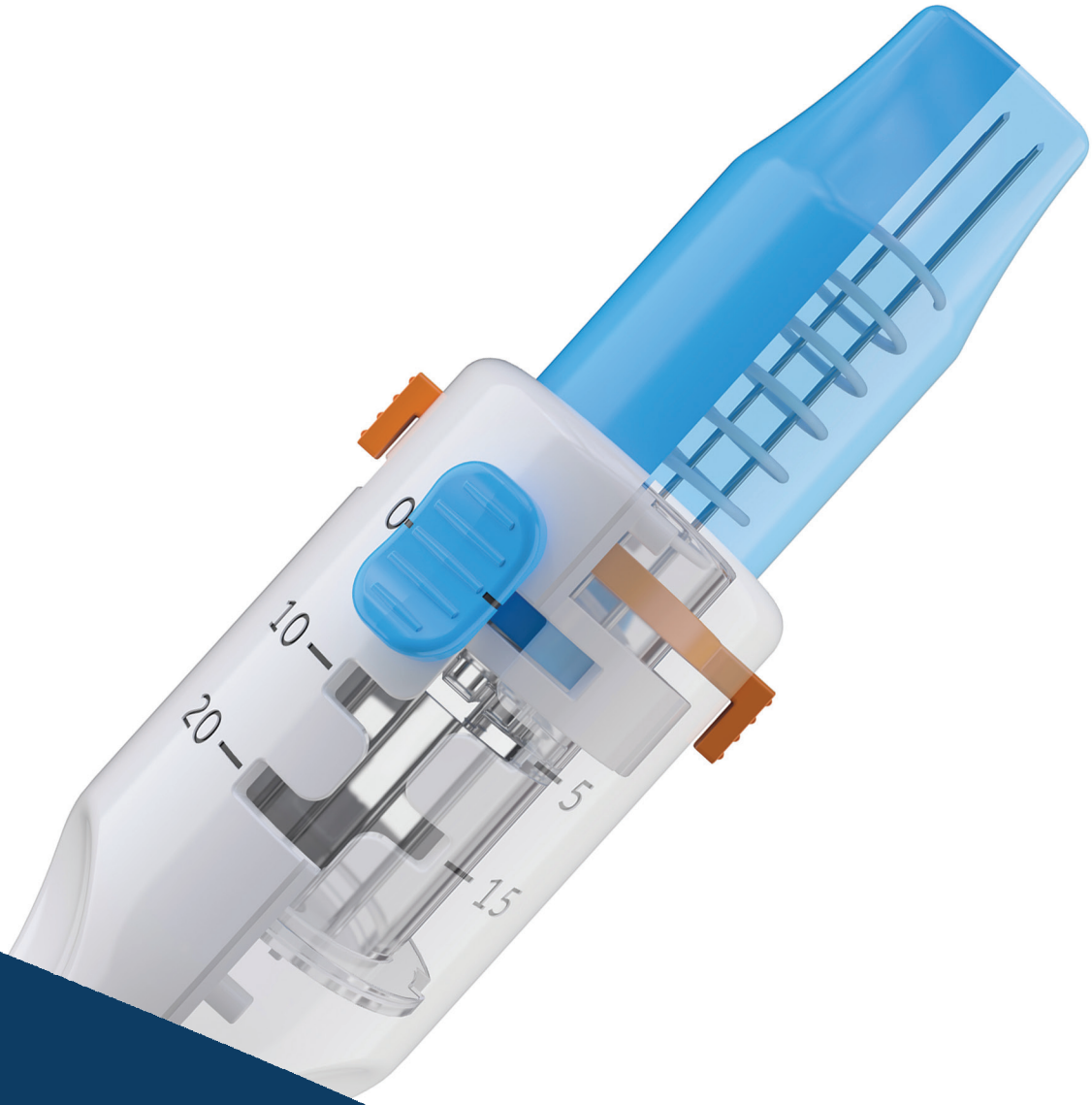
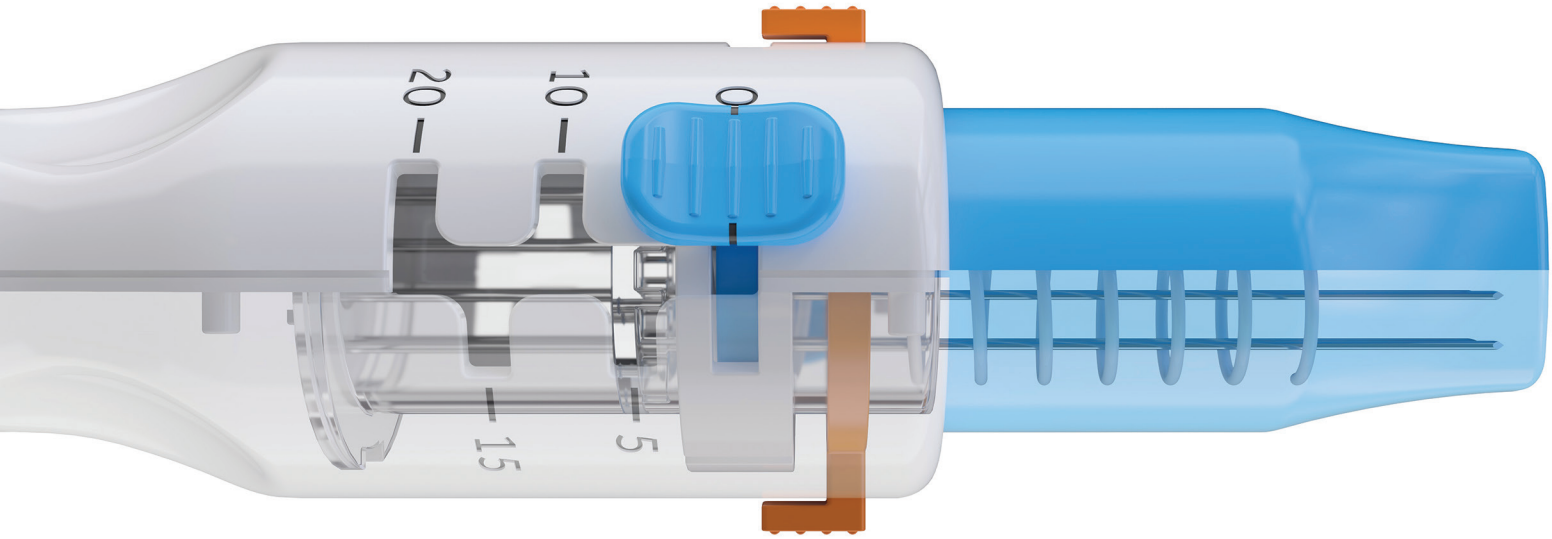


DUOMED

ePORE & CUTIS THERAPY

ON THE PULSE OF PRECISION CANCER TREATMENT

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.

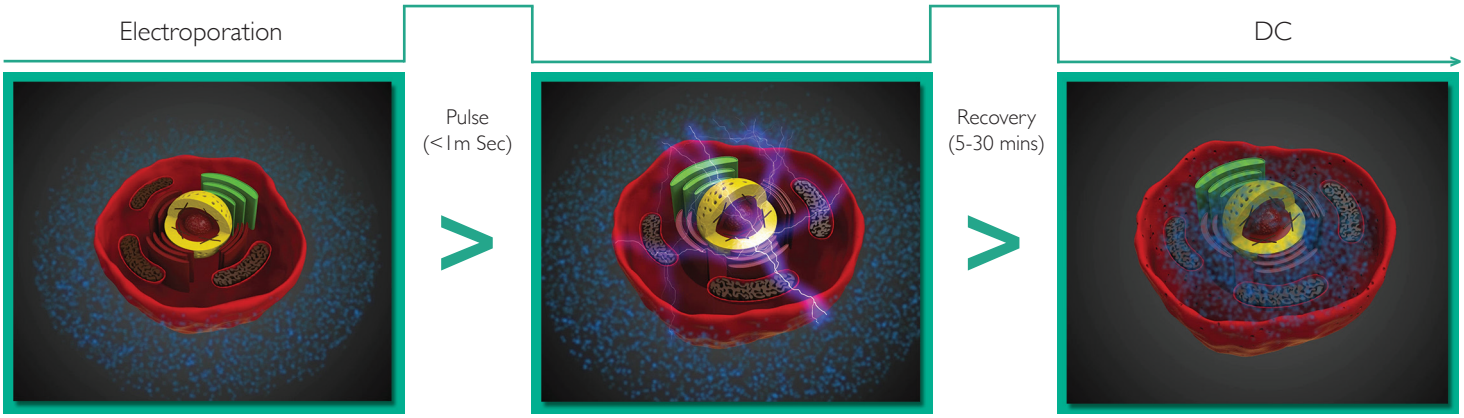
MIRAI MEDICAL has developed an endoscopic approach to target gastrointestinal cancers by utilizing an energy-based technology called electroporation. This treatment approach essentially causes tumour tissue to become extremely porous for several minutes allowing for greater absorption of specific chemotherapy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

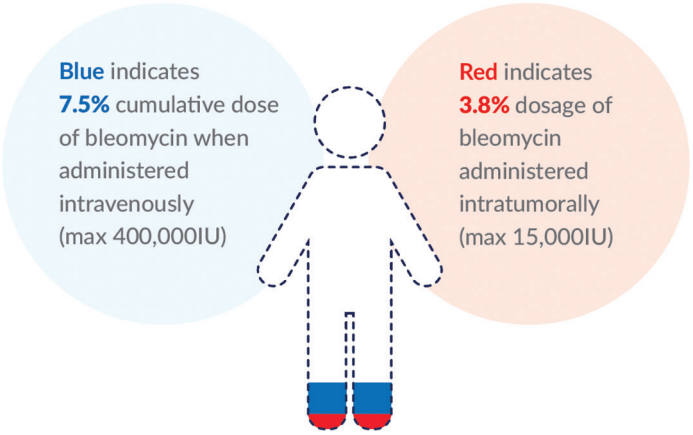
Cell Membrane During Pulse

Cell Membrane After Pulse
(Cell Returned to Original State)

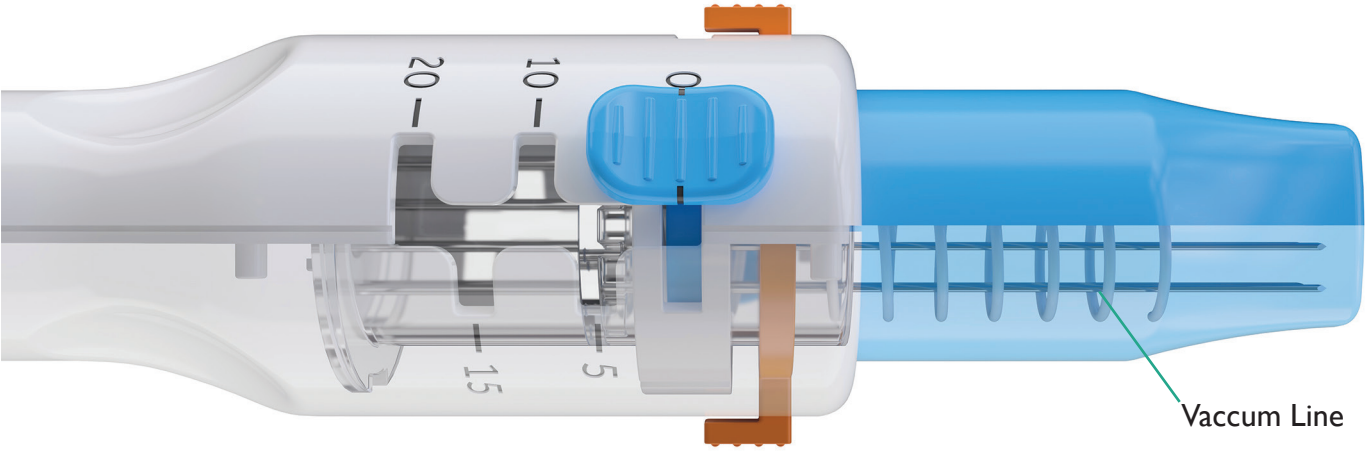
MAXIMUM SAFE CUMULATIVE DOSE OF BLEOMYCIN INTRAVENOUSLY VS INTRATUMORALLY

Electroporation with chemotherapy has been in clinical use for more than 15 years and in 2006 the European Standard Operating Procedure (ESOPE) 1, 2 which described the standard delivery of the procedure including chemotherapy dose. In the last 5 years calcium has been identified as an alternative to chemotherapy.
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.

Electroporation pulses were typically delivered previously at 1Hz or 5KHz. The ePORE® can now deliver these pulses at 250KHz greatly simplifying the delivery and minimizing patient discomfort.



Gehl, J., Sersa, G., Matthiessen, L., Muir, T., Soden, D., Occhini, A., Quaglino, P., Curatolo, P., Campana, L., Kunte, C., Clover, A., Bertino, G., Farricha, V., Odili, J., Dahlstrom, K., Benazzo, M. and Mir, L., 2018. Updated standard operating procedures for electro-chemotherapy of cutaneous tumours and skin metastases. Acta Oncologica, 57(7), pp.874882.



CUTIS ELECTRODE

Taking feedback from experienced clinicians across Europe the CUTIS skin electrode has been designed and engineered with both the clinician and patient in mind.

The retractable head offers unique benefits:

- Needles are fully supported as they enter and penetrate tissue, avoiding needle bending, convergence
- Patients treated under LA do not see the needles, relieving potential anxiety
- Safe - no need for recapping

Advantages of CUTIS & ePORE® Therapy

High frequency electroporation with no muscular contraction

Ability to be delivered under LA in an outpatient setting

Precision delivery of non-thermal ablation

Preservation of healthy tissue

CUTIS and ePORE® are repeatable and leave standard treatment options available

Significant cost savings

ePORE® therapy is an option for patients with cutaneous and subcutaneous accessible lesions up to 20mm in depth.

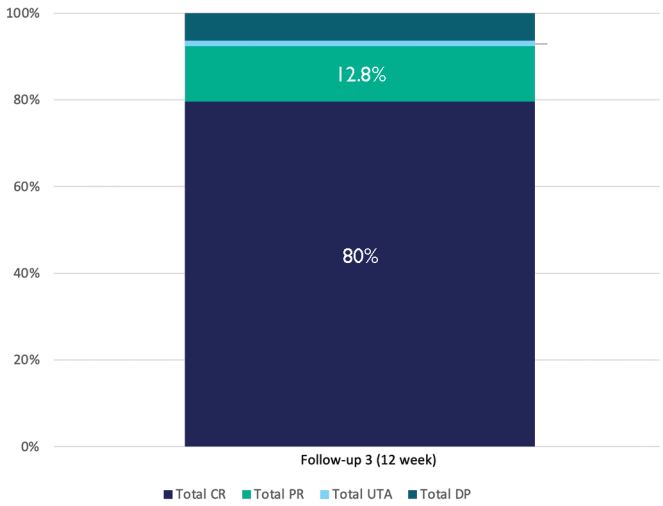
Examples of cutaneous and subcutaneous cancers that can be treated with CUTIS include:

- Non-melanoma skin cancers including BCC, SCC
- Metastatic melanoma
- Cutaneous metastases from other cancers eg. breast cancer
- Rarer malignancies eg. Merkel Cell Carcinoma
- Cutaneous B-cell lymphoma
- Cutaneous gynaecological cancers

BEFORE/AFTER TREATMENT

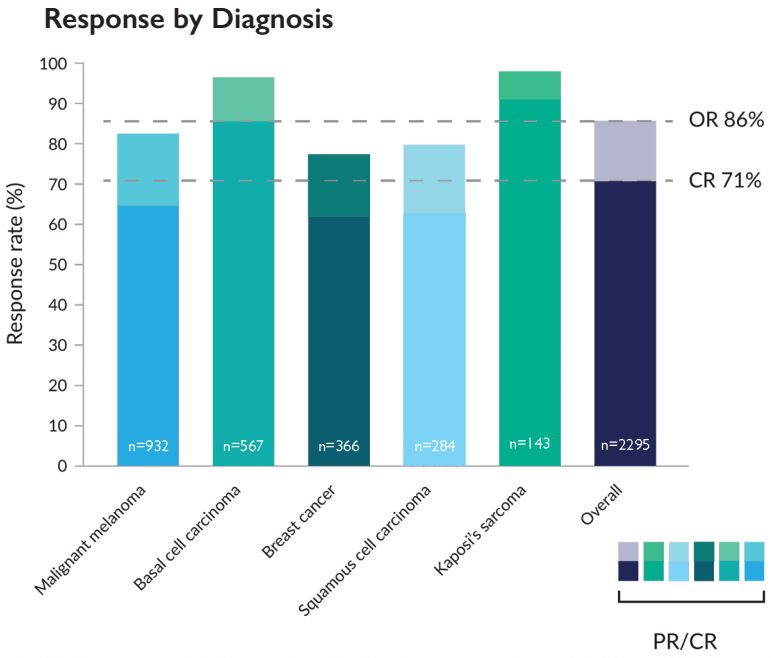
ePORE HF PATIENTS

Percentage Response 12 weeks

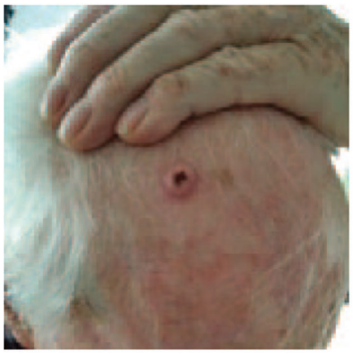


ESOPE ECT PATIENTS

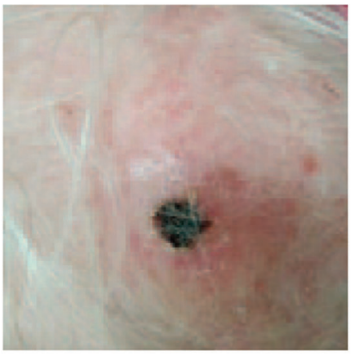
A.J.P. Clover et al. / European Journal of Cancer 138 (2020) 30–40



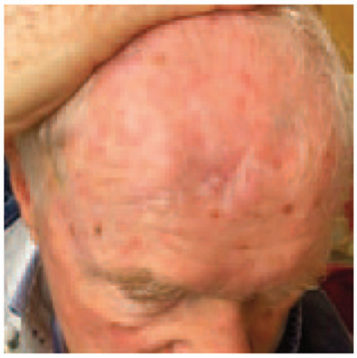
Pre Treatment



4 Weeks



1 Year Follow Up



CR: 79%; PR: 12.8% @ 12wks Patients had failed all other options

FAQ's

Q: What is ePORE® therapy?

The application of pulsed electrical fields directly to tissue will create pores in the cell membrane in a process called 'electroporation'. The pulses are created by the ePORE® generator and we refer to this treatment as ePORE® therapy. Effective treatment requires the electrical pulses to be above a threshold voltage with pulses of shorter duration requiring higher voltages to effect the membrane. Pulse lengths from nanoseconds to microseconds have been shown to impact on both internal organelles and the cell membrane respectively. The greater the number of pulses delivered the larger in number and size of pore created but this is generally limited to avoid heating of the tissue.

Q: Can ePore therapy be repeated?

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 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: What is Electro-chemotherapy and Electro-calcium therapy?

Pulsed electrical fields can be delivered alone to induce local tumour cell death in a process called Irreversible electroporation or when a lower voltage and pulse number are employed the membrane pore formation is reversible and this is typically combined with a drug or molecule such as calcium. These molecules are more easily absorbed by the cell via the pores created in the membrane after the pulsed electrical fields are generated. In the case where the pulsed electrical fields are combined with a chemotherapeutic agent the treatment is referred to as electrochemotherapy with the drug rendered far more effective due to its more direct absorption into the cancer cells. In the case of calcium, its level within the cell is carefully regulated and when an excess is absorbed as is the case after the application of pulsed electrical fields combined with the local injection of calcium into the tumour tissue it can trigger automatic cell death of the tumour.

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: Who is suitable for the treatment?

The clinician will carefully consider the appropriate options for treatment considering the available clinical evidence, guidelines and the underlying health of the patient. In the case of CUTIS and cutaneous or subcutaneous malignancies those typically considered suitable include:

- Elderly patients or those with comorbidities
- Patients considered unsuitable for surgery
- Patients that would be at risk from sedation or general anaesthesia.
- Patients with recurrent disease and where tissue preservation is critical
- Patients where tissue preservation is an important consideration, e.g lesions on the face, or patients with recurrent lesions such as Gorlins syndrome.

ePORE® therapy and CUTIS can also be suitable for patients presenting with:

- Non-melanoma skin cancers including BCC, SCC
- Metastatic melanoma
- Cutaneous metastases from other cancers e.g. breast cancer
- Rarer malignancies e.g. Merkel cell carcinoma
- Cutaneous B-cell lymphoma
- Cutaneous Gynecological cancers

Q: What stage of the disease can be treated?

When utilised to manage late stage disease then the aim is purely quality of life improvement for the patient. For earlier stage disease and basal cell carcinoma the intent is curative and patients should discuss all the available options with their clinician.

ePORE® therapy is ideally suited where tissue preservation and local healing can be challenging post procedure. For patients who present with larger lesions (>3cm), ePORE® therapy can greatly reduce the tumour and provide comfort and a greater quality of life.

Q: What doses of drug 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 maximum dose is 15,000 IU/m2. If injected intratumorally, the dose is 1000 IU/ml.

There are very few side effects associated with the use of bleomycin in combination with ePORE® therapy, as the doses used are ten-fold lower than the standard doses used without electroporation.

In the case of calcium a concentration of 220 mmol has been utilised in clinical studies to date and is injected intralesionally just prior to electroporation. Please refer to our references section for further information.

THE FUTURE OF ePORE® AND ELECTROPORATION

The combination of electroporation and calcium is also an extremely promising area for use with electroporation. Falk et al [3] found in a double blinded randomised phase II study in patients with cutaneous metastases that calcium combined with electroporation is safe and has a similar response rate to bleomycin.

The combination of high frequency electroporation performed under local anaesthetic in an out patient setting opens the door to the use of electroporation earlier in the patients disease state, including patients with premalignant disease and those with benign lesions e.g. keloid scars and vulva intraepithelial neoplasia (VIN).

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