Human Experience with Irreversible Electroporation

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Considering the remarkable opportunities and safety profile demonstrated in the animal studies using irreversible electroporation, it would seem intuitive that this method would provide a safer, more effective and more widely applicable treatment for solid tumours in humans.

The first patients in Australia were recruited in October and November 2008 and the first procedure performed on an elderly Chinese lady with recurrent hepatocellular carcinoma. The procedures were performed in a phase 1 safety trial framework and a number of patients with incurable and widespread malignancies were treated using irreversible electroporation applied by a commercial device (the NanoKnife™). Because of the constraints of the trial, it was decided to limit the application to only liver, lung and kidney tumours. Prior to this trial irreversible electroporation had been performed in humans only in the prostate gland. Unfortunately the prostate gland remains off-limits in our local area because of the multiple competing methods of treatment of prostate cancer localised to the gland.

Once a suitable cohort of volunteers for this new treatment had been obtained, the challenge became how to apply the energy safely and how to ensure that the whole target zone had been treated adequately.

Our experience with interventional radiology and percutaneous procedures over the past 30 years have provided us with sufficient expertise to be able to place either the bipolar or uni-polar electrodes in the desired locations without difficulty.

Just like the animal experiments, we used general anaesthesia with muscular paralysis to ensure that the energy applied to the electrodes did not cause severe muscle contraction. Even with the patient fully paralysed, the energy delivered by the NanoKnife™ is sufficient to cause contraction of a muscle in the immediate vicinity of the electrodes. Additional patient monitoring using BIS monitors and a direct arterial pressure monitor was used as during the application of the electroporation, the electrocardiogram tracing was significantly distorted by the electrical energy. In a few patients, the electrical energy generated extrasystoles and in one patient, a series of contractions which did not provide adequate cardiac output for several seconds.

As a result of these cardiac arrhythmias, an ECG synchronising device was used to deliver the NanoKnife™ energy 50 μs following the peak of the R wave. While this device prevented the arrhythmias, the delivery of the energy was markedly delayed as in most patients only one or two pulses could be delivered per heartbeat. In practice however, the time of delivery of the energy is not a rate limiting factor for the procedure.

B. Rubinsky (Ed.): Irreversible Electroporation, BIOMED, pp. 249–254.
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In the animal experiments, ultrasound was the primary method of localisation for placement of the electrodes. However in humans, especially in the case of metastases from colorectal carcinoma, ultrasound visualisation solutions can be difficult and for this reason, computed tomography was used for our image guidance. This was even more necessary in the lungs and in most of the renal tumours that were treated.

In those patients in whom ultrasound could be used, similar findings in terms of immediate loss of ultrasound echogenicity with electroporation were observed. An unexpected finding was the generation of relatively large amounts of gas immediately adjacent to the electrodes. This gas dissipated quite rapidly into the venous system and did not impact on the imaging, in fact it aided the computed tomography guidance. Without contrast enhancement, and in the absence of gas bubbles, there was no change in tissue attenuation to indicate the treated zone on computed tomography.

The other complicating factor in the group of patients we chose to treat was the inability to reliably place a grid pattern of electrodes over the tumour. This was because of the overlying ribs, scapula and other vital organs. Unlike the prostate, where a rectangular grid could be used to accurately space the electrodes throughout the gland, in the liver, the spacing of the electrodes was usually performed in an oblique manner from a limited access point in the intercostal space. This aspect of the treatment remains the most difficult in terms of planning and execution. As our experience has grown, we have moved from planning a "slab to slab" delivery to planning a "point to point" delivery of electroporation. We have also reduced the electrode exposure from 40 mm to 20 to 30 mm. This has had the additional effect of increasing the resistance of the electrodes and limiting "overcurrent" episodes. Positioning the electrodes through the tumour mass remains the most time-consuming facet of the procedure and in some respects, the more sophisticated electrodes available for competing technologies such as radio frequency ablation make those procedures quicker to perform as the electrode placement is very straightforward.

Early in our experience this resulted in "skip lesions" as the entire tumour had not been completely electroporated. Even now it is still difficult to be sure with electroporation that the entire treatment zone is "dead" at the time of completion. The available current display is simply an indication rather than a guarantee of electroporation and current flow across the tissue. The display gives an indication of the current throughout the length of the pulse and ideally, the current should increase in both across the pulse and across the whole train of pulses.

The promise of preservation of the structural integrity of the tissue was achieved and as a result of this we have been able to place the electrodes in an extremely aggressive manner with respect to vital organs. Where a tumour lies adjacent to a large bile duct, blood vessel or other vital structure, with imaging guidance it is a simple matter to position the electrodes in such a way as not to puncture the vessel or structure yet provide a zone of electroporation which involves the region of three vessel structure. Likewise lesions adjacent to the gall bladder, stomach, diaphragm and right atrium have been accessed effectively without evidence of damage to these adjacent vital structures.

In terms of complications, apart from the cardiac arrhythmias mentioned earlier, there have been no complications directly related to the irreversible electroporation. Cases of haematuria have occurred when the collecting system has been punctured by an electrode and in one patient the left adrenal gland was unintentionally electroporated. The most remarkable feature of recovery following irreversible electroporation

with the NanoKnife™ is the almost complete absence of post-ablation pain. In this group of patients who have been subjected to most other alternatives including chemotherapy, surgery and thermal ablation, this feature of the NanoKnife™ is most remarkable. From a histological point of view, tissue biopsies taken one month after the procedure demonstrated "coagulative necrosis" with preservation of tissue structure. On CT follow-up at periods between one and eight months, there has been no evidence of residual damage to blood blood vessels or bile ducts. Since the biliary endothelium would have suffered the same fate as the tumour cells with electroporation, it is surprising that we have not seen evidence of bile duct stricture. Vascular endothelium and smooth muscle should also be ablated with irreversible electroporation but we have not been able to detect any deleterious effect to blood vessels in our patients. Biochemistry shows marked elevation of the transaminases which resolves to pretreatment levels within 10 to 14 days depending on the volume of tissue treated. In most patients there has been persistent mild elevation of alkaline phosphatase.

Comparison with thermal ablative technologies has been performed indirectly. Where the underlying state of the liver permits, there is a more rapid resolution of irreversible electroporation lesions compared to lesions created by radio frequency ablation. However in patients who have had other treatment modalities and have underlying cirrhosis, resolution of the irreversible electroporation lesions has been slow. Most patients will still show evidence of a zone of ablation on the one-month follow-up computed tomography scan unlike the animal studies where resolution was almost complete at 14 days.

In the kidney, successful irreversible electroporation of an area of tumour results in a focal scar which is almost indistinguishable from the lesions produced by other ablative technologies. The major difference with irreversible electroporation is the ability to treat right into the central portion of the kidney and collecting system without causing thermal damage and late strictures. In the kidney, there has been no postprocedure pain and none of the patients treated have developed a "post-ablation syndrome".

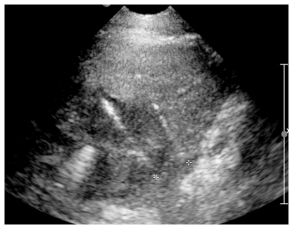
In the lung our experience is still very limited. Pneumothorax is almost inevitable but not unexpected and there is rapid development of airspace consolidation in the treated region. It can be difficult to obtain the same type of current flow across a lung lesion as we have seen in the liver and kidney and to date our clinical response has been disappointing. We have however demonstrated that the treatment can be applied both to the mediastinum and to the hilum of the lung with a high degree of safety. There is a significant application for patients with a limited number of lung metastases provided the technology of electroporation can be improved with respect to the lungs.

Going forward we shall be directing our activities to the liver and kidney for focal tumours that could be potentially cured with one NanoKnife™ procedure. Particularly for those patients who have focal disease, the almost complete lack of toxicity and absence of post-procedure pain from irreversible electroporation with the NanoKnife™ make this procedure most enticing.

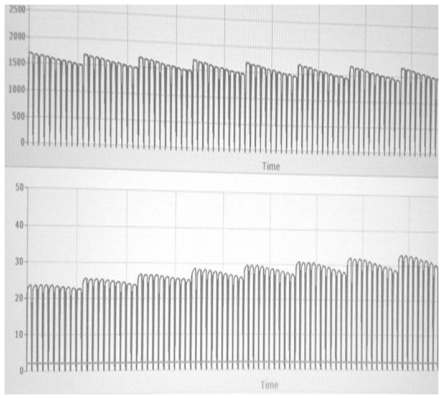
At other sites researchers are beginning to apply this technology in humans in these and other areas including the prostate, pancreas and even the brain. The challenge will be to develop easier electrodes to use and more secure method of measuring the immediate efficacy of the procedure.

Illustrations

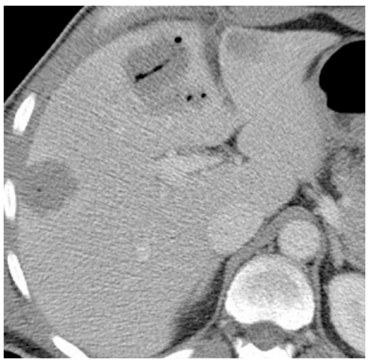
The procedures were done in a CT suite under general anaesthesia. Electrodes were placed with CT and or ultrasound guidance. The author is operating the NanoKnife™



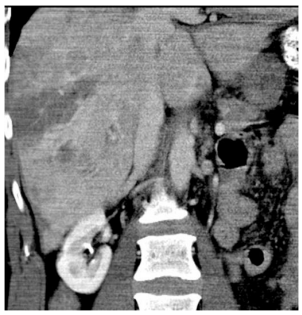
Ultrasound image with two electrodes and their gas bubbles in the plane of view. Echogenic structures to the left and below the electrodes are due to prior electrode activation. It is assumed that the bubbles are generated from electrolytic processes on the electrodes.



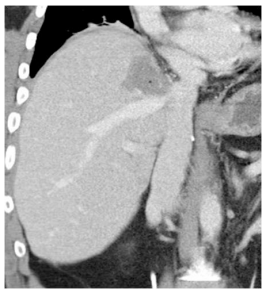
Post electroporation display. Top panel is voltage which falls across each series of pulses as the capacitor discharges. The lower panel shows increasing current flow which indicates electroporation has been achieved. Current is determined by voltage and electrode length (resistance).



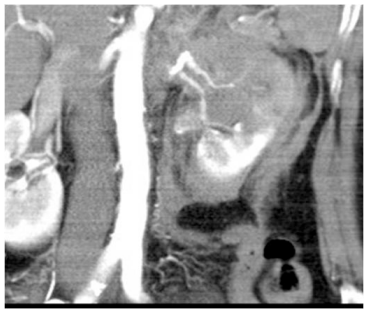
Contrast enhanced (delayed portal venous phase) CT post NanoKnife$^{TM.}$ Electroporated areas show lack of enhancement even though major vessels are still patent.



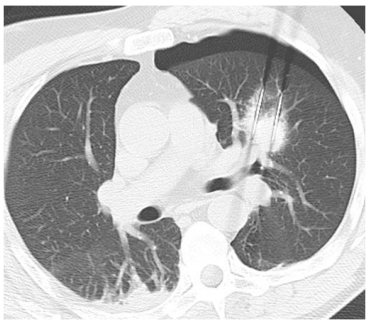
Patient with neuro-endocrine tumours. A large slab of electroporation has been performed. The oblique shape results from an inability to access a grid pattern through rib and intercostal spaces. Note the patent vessels within and at the inferior border of the treated zone on the portal phase CT scan.



Colorectal carcinoma near right atrium, diaphragm and hepatic vein IVC confluence. Successful procedure without damage to these structures and no post procedure pain.



Upper pole "nephrectomy" with the NanoKnife™ for a renal metastasis. Upper pole major arteries are patent at the end of the procedure. Minor haematuria 24 hours. No post procedure pain in spite of minor haemorrhage in the perirenal space.



Solitary hilar metastasis with electrodes in position astride the upper pole pulmonary artery. No haemoptysis after the NanoKnife™ procedure. Pneumothorax resolved on drainage in 24 hours.