Irreversible Electroporation for Treatment of Liver Cancer

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G&H How does the NanoKnife work?

GN The NanoKnife (AngioDynamics) works on the principle of irreversible electroporation (IRE). Using this technology, a cell is subjected to a powerful electrical field using high-voltage direct current (up to 3 kV); this creates multiple holes in the cell membrane and irreversibly damages the cell's homeostasis mechanism, leading to instant cell death. Reversible electroporation—in which up to 1 kV of energy is used to create reversible holes in cell membranes—has been available for some time and is used to enable chemotherapeutic agents to penetrate cells. Research by Rubinsky and colleagues at the University of California, Berkeley showed that increasing the energy to 3 kV resulted in permanent holes that cause cell death.

G&H What are the potential applications of the technology?

GN In most centers, IRE is performed in the liver, kidney, lung, prostate, and pancreas; IRE is also being used to treat metastatic disease in the liver. However, I should note that the US Food and Drug Administration has only approved this technology for soft-tissue applications (under their 510(k) process); use of this technology in organs is currently an off-label application, and we inform all our patients of this fact.

G&H How does IRE differ from radiofrequency ablation or cryotherapy?

GN Radiofrequency ablation (RFA) uses very high levels of heat to burn the cell. There are different technologies for RFA, but the fundamental idea is to use alternating current to create heat that results in cell destruction. With cryoablation, extremely low temperatures are used with a freeze-thaw cycle, which causes the cells to swell and burst. In contrast, IRE using the NanoKnife is a nonthermal method of destroying the cell.

There have been no head-to-head randomized trials comparing these technologies, but my clinical experience with IRE has yielded promising results so far. We have treated several lesions that have responded very well, and most of the patients treated with IRE seem to feel less pain after this procedure than after RFA or other treatments. These findings need to be validated in head-to-head comparisons involving patient groups with similar characteristics, but such studies have not yet been conducted. In the meantime, my colleagues and I are collecting data on all our patients—for example, the amount of pain medication they use and their postoperative pain scores—and we plan to compare these data with information from other patients.

With RFA, the treated area undergoes fibrosis and scarring, so we must wait a long time to see a decrease in the size of the treatment zone. In contrast, several of the lesions that we have treated with the NanoKnife have shown a decrease in the size of the treatment zone as early as 1 month following treatment. Another benefit of IRE compared to RFA is the ability to treat tumors close to blood vessels in the liver. With RFA, we are unable to treat tumors near a major blood vessel because of the “heat sink” effect: The part of the tumor that is near the blood vessel will not be properly treated because heat is lost to the flowing blood. With IRE, however, we have treated lesions in close proximity to vessels; in some cases,
we have even had a vessel running through the treatment zone, and we have not encountered problems with collateral injury or side effects to these vessels. Our experience with IRE is still limited, so we need more time to validate these results.

**G&H** Who are the best candidates for the NanoKnife procedure? In which cases is use of the NanoKnife contraindicated?

**GN** An ideal candidate for IRE should have a tumor located within a specific organ without systemic metastases, and the tumor should meet the size criteria. IRE works best for tumors under 3–4 cm; we have treated larger lesions, but ideal results are obtained in smaller tumors.

In terms of contraindications, we are currently not treating patients with pacemakers or patients who have a history of cardiac arrhythmias or irregular heartbeats, as we have some concerns that IRE might precipitate irregular heartbeats or arrhythmias in these patients. IRE is also contraindicated in patients with extensive disease involvement outside a particular organ; if a patient already has metastases in several other organs, he or she would not be a candidate for the procedure. Finally, patients with extremely large lesions are not ideal candidates for IRE.

**G&H** What are the risks associated with IRE?

**GN** There are risks of bleeding, fistula formation, or infection at any time we insert needles into the body—especially when 2 or 3 needles are used at once. Additionally, because of the high current used with IRE, the procedure carries some risk of precipitating an irregular heartbeat, although use of the Accusync device has markedly decreased the cardiac risk. Finally, use of IRE may involve site-specific risks; if we are treating a lesion in the lung, for example, there is a risk of pneumothorax, or a collapsed lung, which is usually treated with a chest tube. Similarly, if IRE is used to treat a lesion in the kidney, the procedure carries a risk of injury to the ureter or the blood vessels.

**G&H** How do interventional radiologists avoid killing healthy cells surrounding the cancer?

**GN** Needle placement is initially evaluated using a computer software model that is part of the NanoKnife platform; the interventional radiologist enters the coordinates and size of the lesion in 3 dimensions, and the software determines the size of the margin that will be achieved with the treatment. Ideally, we want to include a zone of normal cells in the treatment area; with IRE, we aim for a margin of 0.5–1 cm. Because the computer provides a reasonably accurate estimate of the treatment area, we can avoid unnecessary damage to healthy cells surrounding the tumor.

**G&H** What has been your experience with IRE to date?

**GN** So far, we have treated approximately 100 patients, and we have achieved good results in approximately 65–70% of cases. In some cases, patients who initially had good results showed recurrence over long-term follow-up and required re-treatment; in a few other patients, we achieved only a partial response following the initial treatment.

**G&H** Do you think IRE will grow in popularity?

**GN** Yes, I think this procedure will become more popular. IRE has applications in the pancreas and prostate, sites in which tumors represent significant medical problems. If results with IRE continue to look promising and larger series show an increase in survival, then this procedure will definitely become more popular than it is today.

**G&H** What studies have been conducted to evaluate the NanoKnife?

**GN** Several centers have performed animal studies to evaluate the safety of this technology and the treatment of lesions close to bile ducts or blood vessels. In terms of human studies, a phase I safety study was conducted by Thomson and colleagues at the Alfred Hospital in Melbourne, Australia, and these results will be published in the *Journal of Vascular and Interventional Radiology*. I have also presented some of our data at major meetings; we had a poster presentation at the recent Clinical Interventional Oncology meeting in Miami, Florida and an abstract presentation on our experience using the NanoKnife for hepatocellular carcinoma at the Society of Interventional Radiologists meeting in Chicago, Illinois. We also have an abstract that is being presented at the World Congress on Interventional Oncology meeting in New York City this June. At this time, I do not have data from prospective trials, but I am looking at all my clinical data in a retrospective manner and preparing these results for future publications. There are also prospective trials underway in Europe.

Additionally, the Soft Tissue Ablation Registry has been created among the centers that are currently using this technology in the United States, and publications based on this registry data are being planned. I am the co–primary investigator for the registry and will handle the interventional radiology part of the registry. Martin at the University of Louisville in Kentucky is the primary investigator for the registry. Wong at the Malizia Clinic

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in Atlanta is the primary investigator for the urology and prostate part of the registry. Together, we are trying to compile data from different centers so that we can learn from each other’s experience and draw conclusions from a larger group of patients.

**G&H** Can IRE be used in combination with other therapeutic options?

**GN** Normally, we use RFA in combination with transarterial chemoembolization; this combination has been widely used at several centers around the world. At this point, however, I am not sure how IRE might fit into a combination protocol. We have performed a few cases in which we have used IRE in 1 lobe of the liver and performed arterial treatments in the other lobe of the liver, but we have not yet tried to treat the same lesion with combination therapy.

**G&H** What is the necessary follow-up for these patients?

**GN** We do follow-up imaging at 4 and 8 weeks postprocedure. If the results are good, we then perform 6-month and 1-year follow-up examinations. Currently, we use the modified Response Evaluation Criteria in Solid Tumors system to evaluate response to treatment, and we look for lack of enhancement in the follow-up scans. In a few cases that we have treated with the NanoKnife, we have observed a marked decrease in the size of the treatment zones with follow-up imaging. Given this finding, along with the fact that the changes we see in the NanoKnife post-treatment zone are different than those seen with thermal ablation, more research is needed in order for us to understand follow-up imaging criteria. We also need to determine the adequate timing and the role of positron emission tomography scans in the follow-up algorithm.

**G&H** What future studies of IRE are being planned?

**GN** Several studies are underway in Europe, and we have the NanoKnife registry in the United States. In addition, we are currently writing a study protocol to evaluate the role of the NanoKnife in the management of unresectable pancreatic cancer. In this study, 1 group of patients will receive the standard-of-care treatment (chemotherapy followed by chemotherapy and radiation) while the other group will receive chemotherapy and IRE. Finally, working with our urologists and radiation oncologists, we are considering a potential study of IRE for the treatment of prostate cancer. Currently, we are collecting data—with good follow-up protocols for patients treated with IRE—and I will be looking at all our data in a retrospective fashion to see what conclusions we can draw.

Overall, the promise of IRE is compelling. In particular, treatment of the pancreas is an area of considerable interest; it would be a huge advance if we were able to demonstrate a survival benefit by adding IRE in a patient who was inoperable using conventional techniques.

**Suggested Reading**


