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Liver Function Tests Following Irreversible Electroporation of Liver Tumors: Experience in 174 Procedures

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Irreversible electroporation (IRE) is a relatively new ablation modality that uses electric currents to cause cell death. It is commonly used to treat primary and secondary liver tumors in patients with normal liver function and preexisting cirrhosis. Retrospective analysis of 205 procedures sought to evaluate changes in liver function after IRE. Liver function tests (LFTs) results before and after IRE were evaluated from 174 procedures in 124 patients. Aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase (ALKP), and total bilirubin levels were analyzed. The study was Health Insurance Portability and Accountability Act compliant and institutional review board approved. Informed consent was waived. Changes in LFT results after IRE were compared with baseline and were followed up over time to see if they resolved. Changes were compared with volume of ablation. The greatest perturbations were in transaminase levels. The levels increased sharply within 24 hours after IRE in 129 (74.1%) procedures to extreme levels (more than 20 times the upper limit of normal in one-third of cases). Resolution occurred in 95% and was demonstrated to have occurred by a mean of approximately 10 weeks, many documented as early as 7 days after procedure. ALKP levels elevated in 10% procedures, was slower to increase, and was less likely to resolve. Total bilirubin level demonstrated 2 different patterns of elevation—early and late—and similar to ALKP, it was more likely to remain elevated. There was no increased risk in patients with cirrhosis or cholangiocarcinoma. There was no correlation of levels with volume of ablation. IRE results in significant abnormalities in LFT results, but in most of the cases, these are self-limiting, do not preclude treatment, and are similar to the changes seen after radiofrequency and cryoablation in the liver.

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Introduction

Irreversible electroporation (IRE) is a relatively new ablation technology that is commercially available as the NanoKnife since 2009; it has a Food and Drug Administration 510K approval for soft tissue ablation. Its use in the liver or other organs is considered off-label. Pulses of high-voltage direct current between pairs of electrodes cause cell membranes to spontaneously develop irreversible nanopores, leading to cell death.[1] IRE has the benefit of minimal to no thermal effect and consequent preservation of the collagen matrix that supports sensitive structures such as blood vessels.[2] It has also been demonstrated to be an effective ablation tool with a well-defined ablation zone and successful complete response rates.[3] With these credentials, IRE is an attractive modality to use in the liver for the treatment of malignant liver lesions and has the potential to treat lesions that would be high risk for vascular complications or where other ablation modalities may have limited success.

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Observed but not described in detail is the liver enzyme elevation that occurs after liver IRE.[3] Many patients with liver tumors being treated with IRE may have pre-existing elevation of liver function. Reasons for this include chronic liver disease, concurrent treatments that affect liver function or compromise of the biliary tree. Careful analysis of the effect of IRE on liver function in a large group of patients is important to provide confidence that these patients can be treated with minimal risk and maximal benefit.

Liver enzyme elevation after thermal ablation procedures such as radiofrequency ablation and cryoablation has been described.[4,5] There is self-limited elevation predominantly of transaminase enzymes. Thermal ablation results in necrosis of nontumoral tissues such as bile ducts and blood vessels, which are spared with IRE; hence, the changes in liver function after IRE may be different.

This article evaluates the effect of IRE on liver enzymes during the postablation period in the largest cohort of patients treated at a single institution.

Materials and Methods

All patients undergoing IRE procedures in the liver were included in this institutional review board–approved retrospective analysis. All completed procedures between January 2010 and October 2014 were evaluated. Informed consent was waived. Patients were considered candidates for IRE in the liver if disease was limited (under the Milan criteria in the case of hepatocellular carcinoma [HCC] or similar size or number of lesions in the case of other primary and secondary liver tumors). Contraindications were limited to life-threatening cardiac arrhythmias, automated internal cardiac defibrillator in a place that has demonstrated recent activity, and pacemaker-dependent patients. Preexisting liver disease or elevation of liver enzymes was not a contraindication to IRE.

Procedures were performed using the NanoKnife System (Angiodynamics, Latham, NY) with the patient under general anesthesia and with computed tomography guidance. Having obtained informed consent, general anesthesia was induced and the patient positioned appropriately. A baseline contrast-enhanced computed tomography scan was performed (Siemens Somatom Plus, Siemens Medical Solutions, Malvern, PA) and electrode placement planned using the baseline scan. IRE electrodes were placed to achieve ablation of the entire lesion with a margin of 5-10 mm when possible and maximal debulking of the lesion when complete lesion ablation was not feasible. With the patient paralyzed (zero twitch), electrode pairs were activated in sequence for a total of 70-90 pulses per pair using between 1500 V and 3000 V. After completion of ablation, a postprocedure contrast enhanced computed tomography scan was obtained.

Patients were admitted the day of the procedure, kept overnight, and discharged the following day in most of the cases. If discharge was delayed, it was generally related to pain or prolonged recovery from anesthesia.

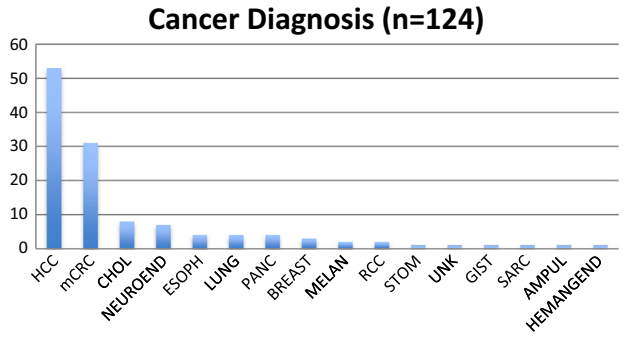

Figure 1 Procedures stratified by cancer diagnosis. (Color version of figure is available online.)

Patients had baseline laboratory assays obtained within 30 days of the procedure. Laboratory assays were performed daily during inpatient status and during follow-up at 4-6 intervals or as clinically indicated. Additional laboratory assays may have been available from laboratory notes from other specialty teams. Changes in liver function tests (LFTs) were considered chronologically after the date of each IRE procedure.

Between January 2010 and October 2014, 205 IRE procedures were performed in 136 patients, with a mean of 1.50 ± 0.84 procedures per patient, range: 1-5 (1, $n = 91$; 2, $n = 31$; 3, $n = 10$; 4, $n = 3$; and 5, $n = 2$). Complete preprocedure and postprocedure laboratory results were available in 174 procedures in 124 patients. These data only were considered further in this analysis.

There were 71 men and 53 women, with mean age of 59.8 ± 11.4 years (range 24-83). The etiology of liver lesions included metastatic disease ($n = 62$, 50.0%), of which colorectal cancer was the most common ($n = 31/62$). Primary liver cancer was detected in 62 patients, HCC in 53 (42.7%), and cholangiocarcinoma in 8 (6.5%), the diagnosis was unknown in 1 patient (Fig. 1).

Comprehensive metabolic panel or LFT results included aspartate transaminase (AST) also known as XXX SGPT, alanine aminotransaminase (ALT) also known as XXX SGOT, alkaline phosphatase (ALKP), and total bilirubin (TBIL) levels. Gamma glutamyl transferase and direct bilirubin levels were not typically measured. An increase in transaminase levels after intervention was considered significant if the elevation was more than double the normal range or more than double the preprocedure baseline level. Return to baseline was defined as values within normal limits or within 10 units of the preprocedure value. Similarly, a doubling of ALKP or TBIL levels with subsequent decrease was considered a procedure-related elevation.

Ablation Volume

One hypothesis is that the degree of elevation of liver enzymes after procedure may be directly related to the volume of ablation. Other studies have sought correlation between the volume of normal tissue ablated, otherwise