COMMENTARY

Navigating the Clinical Translation of Medical Devices: The Case of Radiofrequency Ablation

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INTRODUCTION

The rapid development of novel medical devices has provided healthcare professionals with new invaluable tools to diagnose and treat disease; however, this quick rate of innovation poses several regulatory challenges. In this commentary, we illustrate the history and translation of radiofrequency technology and its application toward the treatment of hepatocellular carcinoma (HCC), detailing obstacles and facilitators that emerged throughout the process in the hopes of highlighting broader lessons that may be applicable to other devices.

RADIOFREQUENCY TECHNOLOGY AND HEPATOCELLULAR CARCINOMA

Hepatocellular carcinoma (HCC) is the third most common cause of cancer death worldwide.1 Although the first-line treatment for HCC is surgical resection or transplantation, only 5–17% of patients are considered good surgical candidates.2,3 Due to comorbidity-related limitations, development of more minimally invasive nonsurgical treatment techniques for hepatic malignancies is attractive. Radiofrequency ablation (RFA) is among the most studied local thermal ablative therapy and is currently one of the preferred treatments for early-stage HCC in patients who are not candidates for surgical resection.2

RFA devices deliver an alternating electric current directly to the tumor through a radiofrequency (RF) probe. Because tissue does not conduct electricity efficiently, frictional agitation of ions in surrounding cells generates heat as they follow the changing polarity of the alternating electrical field. As current density is highest in the small electrode, high temperatures are generated around the electrode, denaturing cellular proteins and producing coagulative necrosis of surrounding tissue.4

Origins of radiofrequency technology

Near the end of the 19th century, French physicist Jacques Arsene d’Arsonval found that AC delivered at frequencies above 10 kHz caused a sensation of warming in the body (Figure 1).5 The invention of the triode vacuum tube by Lee De Forest provided a newfound ability to amplify electrical signals and produce the constant high frequency AC necessary to cut or coagulate tissue.6 Widespread acclaim of RF technology in medicine did not occur until 1926, when Dr Harvey Cushing first used William T. Bovie’s electrosurgical generator (the “Bovie Knife”) to excise a previously inoperable cranial neoplasm.5 Although many changes would be made to improve safety and reliability, the basic technological principles remain the same.

HCC was an attractive choice for RFA, as most patients are not surgical candidates, treatments can be repeated as new lesions arise, and the cirrhotic liver acts as a thermal insulator, which focuses the heat on the tumor. Although early RF technology was promising, its small ablation diameter precluded use in hepatic malignancies. In order to increase this, Goldberg et al.7 explored the use of multiple probe RFA arrays to increase the effective area of necrosis in ex vivo calf livers. A multiple probe array, with spaced probes activated simultaneously, increased the ablation diameter synergistically. A series of incremental improvements quickly followed, such as intraparenchymal saline injection, internally cooled electrodes, and clustered arrays.7

US FOOD AND DRUG ADMINISTRATION APPROVAL AND CLINICAL ADOPTION

As a result of the Medical Device Amendments to the Federal Food, Drug, and Cosmetic, Act Sec. 513, passed in 1976, medical devices are now classified by their respective risk. The US Food and Drug Administration (FDA) defines class I devices as those that pose minimal to moderate risk; these are typically exempt from regulatory oversight. Class II devices pose a higher risk than those in class I; this means that more regulatory oversight is needed to ensure safety and effectiveness of the product. Clearance of these products is through a process known as the 510(k) mechanism. This process is designated for devices intended for human use for which the device is “substantially equivalent” to a predicate; that is, the new device is at least as safe and effective as the named predicate. Finally, class III devices are the highest risk, typically sustaining or supporting a patient’s life; as

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Received 14 July 2017; accepted 29 September 2017; published online on 18 November 2017. doi:10.1111/cts.12516
these post the greatest risk for severe injury, they are subject to the most stringent regulatory oversight. Class III devices must undergo the premarket approval process (PMA), which is the strictest pathway for devices requiring clinical data that prove both the medical device’s safety and effectiveness.

The first RFA device submitted to the FDA, the Cool-tip RF Ablation System, was cleared in 2004. The sponsor of this product submitted it through the 510(k) program, citing the Bovie Knife as a predicate device. As the sponsor was able to put forth a case for substantial equivalence, the company was required to submit manufacturing and biomaterial data necessary to prove its equivalence to the Bovie Knife, but was not required to submit preclinical or clinical data on its safety or effectiveness for FDA clearance.

The 510(k) mechanism has drawn criticism in recent years. Some argue that the program places patients at risk for harm by clearing medical devices whose safety is not properly evaluated. This is due in part to the fact that devices with “substantial equivalence” to predicate devices are examined to determine whether they have the same intended use and/or similar technological characteristics as the predicate devices. If so, then it is assumed that the use of the product raises no new safety or efficacy questions, and fewer clinical investigations are required for clearance that would be required during the PMA process. Furthermore, some contend that clearance of devices in this manner may result in marketing of a product at increased costs without tangible patient benefit. When the Medical Device Amendments were initially passed, most medical devices were not often implanted or used for life-sustaining purposes, and were, therefore, of lower cost to patients.

As technology evolved, more complex devices were developed and brought to market, quickly overwhelming the capacity of the Center for Devices and Radiological Health to review these through the more time-consuming PMA process. In light of this increased burden, the 510(k) mechanism has been praised for efficiently facilitating the clearance of much-needed products for patient use. In 2007, the Government Accountability Office audited the use of the 510(k) process to determine whether it was being used appropriately in the review and oversight of medical devices. The Government Accountability Office determined that 66% of class III and 25% of the class II 510(k) device clearances presented significant risk to the patient and should have been cleared by the more stringent PMA process, indicating that the mechanisms were, on the whole, being used for appropriately classified products.

Challenges in broad indications for use
The indication for which the Cool-Tip RFA device was cleared was for the “percutaneous, laparoscopic, and intraoperative coagulation and ablation of tissue, such as partial or complete ablation of nonresectable liver lesions.” Although ablation of lung tumors was not originally an intended use for RFA devices, the “indication for use” put forth by the company in the original 510(k) clearance was broad; this resulted in a variety of applications that injured several patients with lung tumors. In 2007, the FDA issued a warning regarding such use of RFA devices, stating that, despite its clearance for the indication of “general soft tissue ablation,” the medical device in question had not been cleared for this specific purpose. This illustrates a key lesson from the case of RFA devices, that initially clearing medical devices for more specific indications may help to ensure patient safety, help to build the case for broadening indications for a device, and prevent the need for a warning.

The FDA did state, however, that it could not unequivocally claim that the RFA devices were responsible for the deaths observed, or that this application for RFA is not effective; in short, there was no means to determine if this was the case. This is due in part to the human factors involved in the use of these surgical devices; that is, it is challenging to determine whether the device, its application, or the operator was the root cause for observed adverse events. One way in which this might be teased apart is through examination of the “learning curve” effect. This refers to situations in which the true benefits of a novel intervention or device are temporarily obscured while the operators master its use; this could have proven to be the case with early cases of lung RFA. This interaction between operator and device was recognized during a large-scale multicenter trial for RFA in liver cancer involving 2,320 patients across 41 centers. Centers with less experience in percutaneous techniques encountered a significantly higher rate of death and major complications compared with those who had performed more cases. Therefore, in the study of medical devices, conducting such studies may prove informative in teasing apart whether the device, its application, or the operator is responsible for serious adverse events.

Lessons learned
There are a few key lessons we may take from the translation of RFA devices. First, although sponsors and investigators may be eager to find as many applications for their medical devices as possible, it may be advisable to err on the
side of focusing initially on fewer indications for use, so as to ensure patient safety, improve the ability of device operators to consistently carry out the related procedures, and reduce the potential for a warning. Second, in examining serious adverse events, it can be challenging to determine whether the events are attributable to operator use, application, or the device itself. Conducting retrospective analyses to determine whether a "learning curve" exists with the product may be of use to identify the root cause of the events. As medical devices form and play an increasingly vital role in our medical care, the FDA faces a difficult task in balancing the need for patient safety with promoting technological innovation. Transforming an established regulatory landscape is challenging, but as technology evolves, regulations must adapt as well.

Acknowledgment. The authors wish to acknowledge Elizabeth Eckert for her invaluable recommendations during the research process.

Author Contributions. All author contributed to the writing of the manuscript. A.A.F. designed and performed the research. M.O.V. assisted with performing research and created Figure 1.

Conflict of Interest. The authors declared no conflict of interest.

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