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Research progress and clinical application of cooled radiofrequency ablation

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Highlights

- Cooled radiofrequency ablation (CRFA) represents an advancement in RF ablation, enhancing treatment safety and efficacy through electrode cooling.
- CRFA principles, electrode cooling methods, efficacy evaluation, and an overview of major CRFA devices available on the market are comprehensively analyzed.
- The clinical advancements in applying CRFA technology indicate its feasibility and safety as a viable treatment modality.

Abstract

Radiofrequency ablation (RFA) is a minimally invasive clinical treatment that uses radiofrequency energy to generate heat, resulting in the thermal necrosis of targeted tissues. To enhance the therapeutic benefits of traditional RFA, cooled RFA (CRFA) technology has been developed. CRFA incorporates cooling technology to prevent thermal damage and rapid impedance changes caused by tissue overheating. This review article provides a comprehensive overview of various types of cooling electrode needles used in CRFA, as well as an evaluation of their efficacy and clinical applications. We discuss the advantages of CRFA, including its minimally invasive nature, improved safety profile, and highly effective treatment outcomes. Nevertheless, certain problems and limitations are also addressed to optimize the potential of CRFA as a clinical treatment option. Overall, CRFA has promising prospects. With continued advancements in technology and further research, this innovative treatment modality is expected to significantly impact the treatment of a wide range of medical conditions.

Keywords: Cooled radiofrequency ablation, cooling electrode needle, therapeutic effect evaluation, clinical application

Introduction

Tumor ablation techniques encompass a wide range of methods, including chemical ablation, thermal ablation, irreversible electroporation, and high-intensity focused ultrasound [1].

Chemical ablation, a non-energy-based technique, achieves ablation by injecting ethanol and acetic acid into the tumor, causing coagulative necrosis [2].

Thermal ablation is further divided into radiofrequency ablation (RFA), microwave ablation, cryoablation, and laser ablation. Microwave ablation involves precise insertion of a microwave antenna into the tumor center under visual guidance. The non-insulated tip of the microwave antenna emits electromagnetic waves at frequencies of 915 or 2,450 MHz directly to the tumor tissue, where water molecules intensively collide [3]. This process leads to rapid heating and coagulative necrosis of tumor cells. RFA, recognized for its safety and effectiveness, utilizes radiofrequency energy between 375-500 KHz to heat and destroy diseased tissue and is increasingly used across various clinical settings [4].

Cryoablation employs argon-helium technology, guided by the Joule-Thomson effect, alternating high-pressure argon gas to freeze the tumor

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Table 1. The advantages and disadvantages of different ablation techniques

Ablation technique	The advantages	The disadvantages
Thermal ablation	Cheap Quick and easy Well tolerated	Chemical drugs are not evenly distributed Multiple recurrences Requires multiple treatments
Radiofrequency ablation	Cheap Various electrode shapes The most widely studied and available	The ablation zone is not visible during ablation Thermal sedimentation effect Finite ablation zone
Microwave ablation	High temperature Large ablation area Short ablation time	General anesthesia More difficult than radiofrequency ablation Easily damage healthy organs and tissues
Cryoablation	The ablation zone is visible during ablation Reduce pain	Long ablation time High risk of bleeding The possibility of hypothermia shock
Laser ablation	Precise positioning, suitable for high-risk locations Reduce image artifacts	Small ablation area Limited energy penetration
Irreversible electroporation	Short ablation time Retain adjacent organizational structures Clearly define the ablation zone	General anesthesia The single ablation volume is small
High-intensity focused ultrasound	Non-invasive, in vitro	The patient needs to be still Long treatment time

to -140 °C and helium to rapidly reheat it to 40 °C. This freeze-thaw cycle causes protein denaturation, cellular dehydration, membrane rupture, and thrombosis in microvessels, culminating in the destruction of tumor cells [5-7].

Irreversible electroporation, an innovative ablation technique, uses high-voltage, low-energy direct currents to create nanoscale pores on the cell membrane, disrupting cellular homeostasis and inducing apoptosis [8].

High-intensity focused ultrasound takes advantage of the unique characteristics of sound waves with frequencies between 0.8 and 3.5 MHz. These sound waves are enhanced and focused on a specific distance from the transducer. By using sound energy (up to 10,000 W/cm^2), intense tissue movement is induced, generating heat and causing necrosis at the target location [9].

Cooled RFA (CRFA) offers comparable safety to traditional RFA [10]. It improves treatment outcomes by incorporating cooling functionality to the electrode needle based on RFA technology. This innovative approach has found widespread application in various clinical settings. This review aims to outline the research progress and clinical applications of CRFA. **Table 1** shows the advantages and disadvantages of different ablation techniques.

The principle of CRFA

The treatment mechanisms of CRFA and RFA share a common foundation, employing thermal effects for the ablation of pathological tissues. A closed circuit is formed between the ablation device and the target tissue during the ablation process. As the alternating current flows through the tissue, rapid fluctuations in the electromagnetic field cause polar water molecules within the tissue to oscillate at high speeds. This motion generates heat that triggers the evaporation, drying, shrinkage, and shedding of water within and surrounding the cells, ultimately resulting in sterile necrosis and achieving the desired therapeutic effect [11].

In monopolar ablation, the circuit current flows between the electrode needle and the negative plate; while in bipolar ablation, the circuit current flows back and forth between the two electrode needles, which act as the anode and cathode of the ablation [12]. In multistage ablation, multiple bipolar applicators are used in conjunction to enhance thermal effect and create a larger spherical coagulation zone [13].

The energy generator of the ablation device produces high frequency alternating current. As the current changes, the ions within the tissue interact and produce heat, which raises the temperature of the lesion tissue to above 60

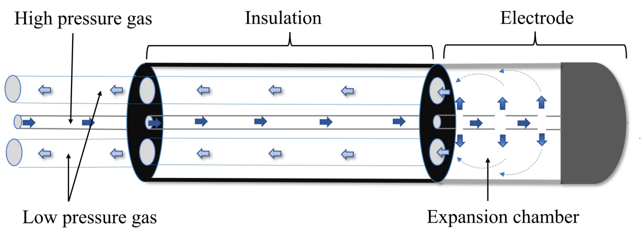

Figure 1. Schematic diagram of air-cooled electrode needle.

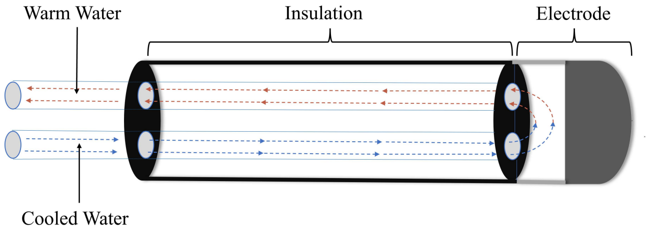

Figure 2. Schematic diagram of liquid-cooled electrode needle.

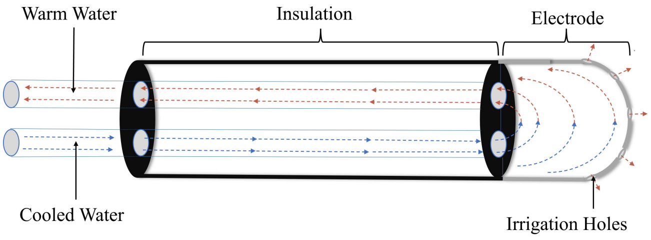

Figure 3. Schematic diagram of the cold and wet electrode needle.

°C, inflicting irreversible tissue damage [14]. However, traditional RFA has a crucial limitation. Tissue in contact with the electrode needle is prone to excessive heat and carbonization, leading to thrombus formation, eschar, and carbonization on the electrode surface. This can affect energy output and ablation efficacy. To address these issues, cold pole RFA system was developed to improve ablation efficiency and surgical success rates. CRFA lowers the temperature of tissues near the radiofrequency electrode, reduces the surrounding tissue carbonization, and achieves a larger necrotic area [15].

Types of electrodes in CRFA and their efficacy evaluation

Types of cooling electrode needles

Based on the cooling method, cooling electrode needles can be divided into internally and externally cooled electrode needles. Internally cooled electrode needles utilize gas or liquid within the device to dissipate thermal energy from the electrode needle through heat transfer, thereby achieving the desired cooling effect. Hence, internal cooling electrode needles encompass both gas-cooled and liquid-cooled electrode needles. In contrast, externally cooled electrode needles exclusively employ cooling liquid as the cooling medium, inheriting the advantages of interior cooling electrode needles while incorporating flushing holes around the electrode.

The air-cooled electrode needle RF system utilizes pressurized CO_2, N_2, or CO as a cooling medium, which is released through a standard gas cylinder, pressure tube, switch, and pressure regulator. As shown in **Figure 1**, the gas flows through a nozzle in the electrode needle into the expansion chamber, where the Joule-Thompson principle produces a cooling effect to cool the electrode needle [16, 17]. Early studies have shown promising results for air-cooled RFA. Carrara et al. used this technique to ablate the liver and spleen of pigs, followed by pathological and histological analysis of each ablation, confirming its feasibility and safety [18]. Similarly, Rempp et al. demonstrated that cryogenic air-cooled radiofrequency electrodes produced a more extensive ablation range and lowered ellipse index than conventional RFA in ex vivo bovine liver; they also observed that increasing power with stable air pressure and standardized application time increased the short axis of the ablation range [19]. Further, Hoffmann et al. used air-cooled ablation electrodes in ex vivo bovine liver and found that impedance-controlled ablation resulted in a maximum short axis diameter of 51.1mm for the ablation zone [20]. These results indicate the potential of air-cooled electrode needle RF systems in ablation and pave the way for further studies to explore its safety and efficacy.

As illustrated in **Figure 2**, the liquid-cooled electrode needle ablation system utilizes an internal tube to circulate cold saline or chilled water into the electrode needle via a perfusion pump. This type of electrode needle, exemplified by the Valleylab electrode needle, is widely used in clinical practice, where cooling fluid remains isolated from both the bloodstream and the tissue targeted for ablation. The system expels the heated effluent through an outflow tube to an external collection unit, effectively cooling the electrode tip internally and moderating the temperature of both the electrode tip and adjacent tissue [21]. The liquid-cooled electrode ablation covers a larger area than conventional

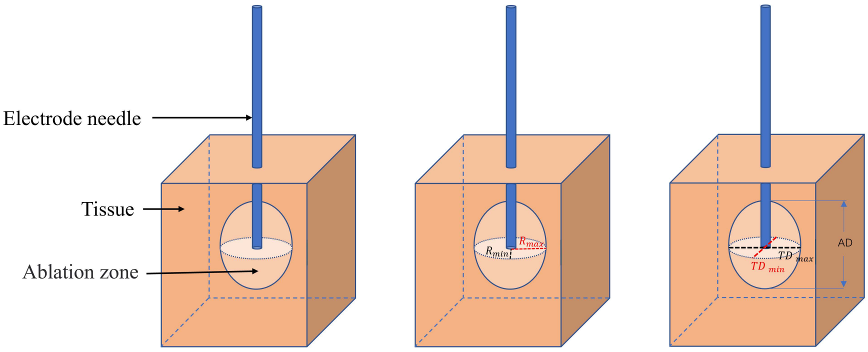

Figure 4. Schematic diagram of ablation evaluation. TD, transverse diameter.

RFA, offering a simple, cost-effective method for producing larger, more spherical lesions [22-23]. Solbiati et al. used internal cooling electrodes in 22 patients who were followed for at least five years, and demonstrated that using an optimized algorithm with a single internally cooled electrode to deliver RF energy to liver tumors produced a more significant, relatively spherical, and reproducible necrotic volume with more prolonged electrode tip exposure [24]. This approach can reduce ablation duration and increase ablation size with minimal adverse event rates. Yu et al. used an internally cooled directional electrode for ablation, producing a hemispherical ablation area that minimized thermal damage to adjacent organs by not extending beyond the hemisphere opposite the needle insertion site [25].

The efficacy of ablation using an external cold-cooled electrode needle (also known as a cold-wet electrode) has also been well-documented. **Figure 3** illustrates the technique, which incorporates a cooling electrode and a hole for cold saline rinsing, directly flushing the electrode tip and the surrounding tissue. The initial cold-wet electrode contained two coaxial cavities and a single saline channel, delivering coolant at a rate of at 40 ml/min and saline at 1 ml/min. This design improved the electrical and thermal conductivity of the tissue, significantly enhancing radiofrequency energy transmission and expanding the damage range [26]. Later improvements to the wet electrode design introduced a single cavity with two micropores at its tip. Additionally, the infusion rates for both coolant and saline were increased to 100-120 ml/min and 1-1.2 ml/min, respectively, creating a broader and more circular ablation area than the closed internal cold electrode, thus further enhancing the procedure precision [27, 28]. Cha et al. conducted an ex vivo study comparing double cold and wet electrodes with double internal cold electrodes, finding that double cold and wet electrodes created more spheres and larger ablation areas [29]. It is critical, however, for physicians to ensure that saline is precisely applied within the designated treatment area to prevent the spread of current and reduce potential complications [30].

CRFA therapeutic effect evaluation

Utilizing the cooled electrode probe in CRFA technology enables the maintenance of low temperatures over extended periods, ultimately resulting in a more expansive and evenly distributed ablation area. When being applied to tumor ablation in liver, kidney, heart, prostate, and other organs, CRFA ensures complete and homogeneous cell destruction. This is evident by a white tissue appearance after lesion cauterization, in contrast to the surrounding healthy tissue that appear darker red [31].

As depicted in **Figure 4**, the ablation range typically exhibits shapes like circular, elliptical, and conical. The ellipticity index (EI) is calculated using the formula EI=2AD/(TD_{max} + TD_{min}), and the regularity index (RI) is determined by RI= R_{min}/R_{max} . For an ideal ellipse, the ablation volume can be expressed as $\frac{\pi}{6} * AD * TD_{max} * TD_{min}$ (AD and TD refer to axial diameter and transverse diameter). Here, the maximum transverse diameter TD_{max} refers to the maximum distance between two opposite edges of the re-assembled coagulation zone in the transverse plane. The minimum transverse diameter TD_{min} represents the minimum distance between two opposite edges of the coagulation zone in the transverse plane, measured in millimeters [32]. These measurements are taken at the midpoint, intersecting the line of the maximum transverse diameter. The AD is defined as the distance between the proximal and distal edges of the clotting region on the axis of the electrode. The maximum radius R_{max} denotes the maximum distance between the electrode axis and the edges of the coagulation zone in the transverse plane. The minimum radius R_{min} is the minimum distance between the electrode axis and the edge of the solidification zone in the transverse plane [16, 19, 22, 25, 33]. In *ex vivo* bovine liver, Clasen et al. conducted multipolar RFA and determined the relationship between coagulation volume and applied energy using nonlinear regression analysis, yielding a linear function V=0.61E+40.7 (r^2 = 0.87) for calculating coagulation volume [34].

Several major CRFA equipment on the domestic and foreign markets

Presently, RFA stands as the prevalent ablative technique in the market, whereas CRFA, despite its later emergence, currently holds a smaller market share. Nevertheless, CRFA exhibits advantages such as reduced patient pain and fewer complications during the treatment process, rendering it a promising avenue for future growth. The cooling electrode needles, composed of a needle tip, handle, catheter, and connector, serve as a fundamental component of CRFA surgical equipment. Globally, major suppliers of CRFA needles include Boston Scientific and Medtronic from the United States, AtriCure from the United States, HealthTronics from the United States, Erbe from Germany, and IceCure Medical from Israel. Within China, suppliers like HYGEA and Surgnova are gaining recognition.

The COOLIEF* Cooling Radiofrequency System (Avanos Medical, Alpharetta, America) is a minimally invasive therapeutic ablation system specifically designed to target neural pain signals. It comprises an 80W radiofrequency generator, peristaltic pump, and treatment cable that capable of creating large-volume spherical ablation areas within nerve and intervertebral disc tissues without increasing the risk of adjacent tissue damage. While heating neural tissue, the system circulates water through the device, flowing through the tip of the RFA probe to keep it at a lower temperature, creating a larger treatment area compared to traditional RFA therapies [35]. This unique patented water-cooling technology has broadened the scope of radiofrequency treatments for chronic spinal, knee, and hip joint pain, contributing to an improved quality of life for patients.

The OSTEOCOOL™ Radiofrequency Ablation System (Boston Scientific, Marlborough, America) is a coaxial bipolar RFA device with a cooling apparatus in its radiofrequency tip. The radiofrequency device operates at a frequency of 468 KHz with a maximum output power of 50W. In a preclinical evaluation experiment on pig cervical spines, Pezeshki et al. utilized this system and demonstrated its capability to achieve large and reproducible ablation zones [36]. Importantly, the system effectively confined the ablation area within the vertebrae, without causing damage to nearby tissues or the spinal cord.

The Cool-tip™ Radiofrequency Ablation System E-Series (Medtronic, Dublin, America) is an internally cooled thermal ablation system designed for soft tissue tumors. The E-Series offers enhanced needle design and increased energy delivery. In comparison to other RFA systems, it can create a larger ablation area in a shorter time frame. This device enables real-time monitoring of temperatures near the ablation zone. Zhang et al. conducted a series of studies using this equipment on pig liver tissue, demonstrating that temperature monitoring in the ablation area is crucial for increasing the size of the coagulation zone [37].

The Dophi™ R150E Radiofrequency Ablation System (Surgnova, Beijing, China) can achieve both individual and simultaneous ablations with three needles. The system, equipped with a Swiss Watson Marlow water-cooling pump internally, reduces carbonization, ensuring efficient energy transmission, maximizes the ablation area, and concurrently minimizes thermal damage. This feature enhances the protection of surrounding neurovascular tissues, showcasing the system's capacity to balance effective energy delivery and tissue preservation.

The rapid development of CRFA, noted for its minimal thermal damage and effective tumor destruction, has led to a diverse range of devices now available on the market. **Table 2** presents several commonly used CRFA devices in the markets worldwide.

Progress in the clinical application of CRFA

CRFA is a well-established modality for the treatment of liver cancer. Multipolar RFA, commonly used for small to medium-sized liver cancers, can sometimes result in overheating, leading to carbonation and rapid impedance rise. In contrast, traditional monopolar RFA requires overlapping techniques to achieve a sufficient ablation margin. Still, microbubbles during RFA can make it challenging to reposition the electrode accurately, leading to incomplete tumor ablation and higher recurrence risk [38]. Rhim et al. demonstrated the feasibility, safety, and efficacy of ultrasound-guided percutaneous RF ablation combined with artificial ascites for treating hepatocellular carcinoma (HCC) in the hepatic dome, with promising results over a 281.4-day follow-up period [39]. Tang et al. reported high complete ablation rates for liver tumors of varying sizes using ultrasound-guided cold needle RFA under local anesthesia, with low complication rates [40]. Clasen et al. further explored the use of MRI to guide the placement of a cooling electrode for treating HCC, achieving a high success rate with minimal complications, underscoring the

Table 2. Several commonly used cooled radiofrequency ablation devices

Company	Cooled radiofrequency ablation equipment	Type of cooling	Electrode needle
Avanos Medical	COOLIEF Radiofrequency system	Liquid-cooled closed-loop internal cooling	Bipolar
Baylis Medical Company	OSTEOCOOL™ Radiofrequency Ablation System	Liquid-cooled closed-loop internal cooling	Bipolar
Medtronic	Cool-tip™ RF Ablation System E Series	Liquid-cooled closed-loop internal cooling	Single/ Multiple
Boston Scientific	Chilli II™ Cooled Ablation Catheter	Liquid-cooled closed-loop internal cooling / Liquid-cooled open perfusion	Single/ Multiple
IceCure Medical	The ProSense™ Cryoablation System	Liquid nitrogen internal cooling	Single
Surgnova	Dophi™ R150E	Liquid-cooled closed-loop internal cooling	Single/ Multiple
Everpace	IceMagic® Cooled ablation equipment	Liquid-cooled open perfusion	Single

RF, radiofrequency.

potential of MR-guided RFA as a promising option for the treatment of HCC [41]. Collectively, these results suggest that CRFA, enhanced by multiple guidance modalities, is clinically effective in the long-term treatment of HCC and is constantly being explored and innovated to promote the development of local tumor ablation. Additionally, CRFA continues to evolve in other clinical treatments [24, 42-44].

CRFA has emerged as a promising alternative therapy for benign and malignant thyroid nodules. In this outpatient procedure, electrodes are inserted through the skin of the neck under ultrasound guidance to rapidly heat the treatment area. This treatment involves gradually moving the electrodes from the medial to the lateral side of nodule while slowly retracting them toward the surface [45]. Jeong et al. evaluated the safety and efficacy of this approach using internally cooled electrodes and discovered that a remarkable 91.06% of nodules experienced a volume reduction exceeding 50% over a follow-up period ranging from 1 to 41 months, with 27.81% of the nodules completely disappeared [46]. Despite temporary complications such as pain, hematoma, and voice changes, which resolved within one to two months, CRFA was demonstrated to be a safe treatment option for thyroid nodules, although long-term follow-up is necessary to confirm these findings. In another retrospective study by Lim et al., the long-term outcomes of CRFA for benign thyroid nodules were investigated [47]. The study included 111 patients with benign non-functioning nodules, who were treated with a cooled tip radiofrequency system and followed up for a minimum of 3 years. The results demonstrated a mean nodule volume reduction of (93.4 ± 11.7)%, a regeneration rate of 5.6% and an overall complication rate of 3.6%. Furthermore, CRFA has also been effectively used to treat large thyroid nodules, benign thyroid nodules in children and adolescents, small follicular tumors, and even low-risk small thyroid cancers [48-51]. Despite these promising findings, there remains variability in treatment parameters such as the number of sessions, energy delivered, and follow-up duration. Therefore, continued long-term follow-up is needed to validate the safety and efficacy of CRFA. Nevertheless, CRFA holds excellent promise as a safe and effective alternative to surgery for treating thyroid nodules.

CRFA offers a less invasive alternative to surgery for chronic sacroiliac joint pain, producing better outcomes than traditional treatments involving steroid and anesthetic injections. Several case series have reported successful results using CRFA in the sacroiliac joint. Notably, in the study of Kapural et al., they reported retrospective observational data on pain relief and functional changes after denervation with CRFA [52]. Their study, which included 27 patients, revealed a notable reduction in opioid use and clinically significant levels of pain relief and operational improvement at 3-4 months follow-up. Cheng et al. were the first to compare the effectiveness of lateral branch CRFA with conventional RFA for sacroiliac joint pain in a clinical study [53]. In their study, data from

88 patients between January 2006 and June 2009 were retrospectively analyzed, without any evidence showing that lateral branch CRFA provided longer-term relief of sacroiliac joint pain than conventional RFA. However, Tinnirello et al. conducted a follow-up in 43 patients who received CRFA versus conventional RFA to denervate the sacroiliac joint and found that patients receiving CRFA experienced more significant pain relief than patients with traditional RFA [54]. The most remarkable analgesic differences occurred at 6 and 12 months.

In 2016, Cheng et al. further explored the use of bipolar RFA in treating 31 patients with sacroiliac joint pain [55]. Their analysis revealed a cost savings of over $1000 per patient when compared to CRFA. Kurklinsky et al. analyzed the electronic records of 41 adult patients who underwent successful CRFA treatment, and found that the medical costs decreased by 51.0% after the initial CRFA and by 70.4% after subsequent CRFA procedures [56]. Although these studies highlight that CRFA is a promising option for chronic sacroiliac joint pain, more randomized controlled trials are needed to establish its superiority over other radiofrequency denervation options.

In recent years, encouraging advancements have been achieved in treating knee pain associated with osteoarthritis by CRFA. This innovative method uses thermal ablation to disrupt the pain signals transmission by sensory nerves in knee. Lash et al. proved the efficacy of CRFA in relieving pain and improving joint function in 51 patients through precisely locating the target nerve and positioning the electrode needle for surgical intervention under ultrasound guidance [57]. In another study, Davis et al. compared the effectiveness of CRFA and intra-articular steroid injections in treating chronic knee pain among 151 patients [58]. Their findings revealed that CRFA provided significantly better pain relief, with 74.1% of patients experiencing a significant reduction in pain at six months, compared to only 16.2% with intra-articular steroid. Moreover, CRFA offers a long-term treatment option for the control and improvement of knee osteoarthritis. This is evident from studies indicating that 65% and 61% of patients achieved significant pain reduction at 12 and 24 months, respectively [59, 60]. Collectively, these studies underscore the potential of CRFA as an effective and sustainable treatment option for patients suffering from knee pain caused by osteoarthritis.

In addition to its aforementioned clinical applications, CRFA has also shown lasting clinical benefits in treating conditions like osteoid osteoma and cancers of the spine, kidney, heart, hip, lung, pancreas, and breast. CRFA technique outperforms standard RF ablation in overcoming the physiological limitations. By delivering higher energy to the surrounding tissues, it creates larger lesions and more extensive tissue disruption, thus leading to durable clinical outcomes. Nevertheless, comprehensive evaluations including extended follow-up periods and additional research are still crucial for determining overall medical costs, survival rates, local recurrence rates, complication rates, disease-free survival rates, and mortality rates of patients. Such studies are essential to fully understand the clinical implications and long-term benefits of CRFA in these medical applications.

Conclusion

CRFA represents an improvement in the field of traditional RFA by incorporating air or liquid cooling mechanisms to lower the temperature of the tip of electrode needle during the standard RFA procedure. The cooling technology minimizes the charring of surrounding biological tissues, allowing for the unimpeded and prolonged output of radiofrequency energy, expanding the range of tumor ablation. Currently, most RFA devices in the market are equipped electrode cooling technology, significantly enhancing the safety and effectiveness of tumor treatment.

Numerous clinical applications have demonstrated the feasibility and safety of CRFA as a viable treatment modality. Nonetheless, the ongoing need for further research remains paramount to delve deeper into various aspects of CRFA, including survival rates, local recurrence rates, complication occurrence rates, disease-free survival rates, mortality rates, etc. The ultimate goal of these continued research efforts is to make CRFA more accessible and affordable, ultimately extending its reach to a broader patient population.

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