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Research progress on simulation of radiofrequency ablation for liver cancer treatment

Shaobo Wang[1], Yuan Yao[2], Haipo Cui[1]

[1]Shanghai Institute for Minimally Invasive Therapy, University of Shanghai for Science and Technology, Shanghai 200093, China. [2]Shanghai Songyu Medical Device Co., Ltd., Shanghai 200050, China.

Corresponding author: Haipo Cui.

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Highlights

- Analyzing the influence of biological tissue parameters on the effectiveness of radiofrequency ablation.
- Comparing the advantages and limitations of four biological heat transfer models.
- Comparing three evaluation methods for assessing ablation-induced thermal damage.

Abstract

Radiofrequency ablation (RFA) is a widely used minimally invasive treatment for non-surgical hepatocellular carcinoma. This review synthesizes the technical principles, core components, and key modeling aspects of RFA. RFA induces tumor necrosis via Joule heating from ionic vibration. Electrode needle design critically impacts ablation efficacy and safety, with multipolar needles offering larger zones yet posing power and tissue risks. Crucially, biological tissue parameters exhibit dynamic spatial and thermal variations, necessitating nonlinear modeling for accurate temperature prediction. While the Pennes bioheat model remains mainstream for its simplicity, more advanced models (e.g., porous medium) enhance physiological realism. Thermal damage assessment commonly employs the Arrhenius model and isothermal thresholds, aided by real-time monitoring for intraoperative precision. Future research should prioritize the development of smart electrodes, creation of personalized tissue parameter databases, and exploration of multi-energy techniques to shift RFA from an “empirically oriented” approach to an “accurate prediction” paradigm, ultimately improving hepatocellular carcinoma patient survival and quality of life.

Keywords: Radiofrequency ablation, liver cancer, electron spin, biological heat transfer equation

Introduction

Cancer is a major disease threatening human life and health, characterized by high malignancy and rapid growth. Among cancer types, primary liver cancer is one of the most common malignant tumors, primarily classified into hepatocellular carcinoma and intrahepatic cholangiocarcinoma, with hepatocellular carcinoma accounting for 70%-80% of the cases [1-4]. The main treatment methods for hepatic tumors include surgical resection, radiotherapy, chemotherapy, and thermal ablation, with resection, radiotherapy and chemotherapy still being the preferred choices in clinical practice [5]. Although surgery can directly resect the tumors, it presents high risks in cases involving tumors in challenging locations, large tumor size, or patients in poor physical condition. In such cases, complete tumor resection may not be achievable. Radiotherapy, while effective for some tumors, can cause damage to surrounding normal tissues and may fail to completely eradicate the tumor [6]. With the continuous development of minimally invasive therapies, local thermal ablation techniques have become an effective treatment for liver cancer [7, 8].

Address correspondence to: Haipo Cui, Shanghai Institute for Minimally Invasive Therapy, University of Shanghai for Science and Technology, Shanghai 200093 Jungong Road, China. E-mail: h_b_cui@163.com.

Local ablation techniques mainly include microwave ablation, laser ablation, and radiofrequency ablation (RFA) [9-11]. RFA, first used in the treatment of liver tumors in the 1990s, is a thermal coagulation technique. It offers the advantages of minimal invasion, high safety, effectiveness, simple operation, and high reproducibility, making it the first-line non-surgical treatment for hepatocellular carcinoma [12-14].

However, efficacy of RFA is highly dependent on the precise prediction of thermal distribution and ablation zones [13]. The complex biophysical interactions during RFA, including dynamic variations in tissue parameters (e.g., electrical/thermal conductivity, blood perfusion), heat-sink effects near blood vessels, and nonlinear thermal damage thresholds, pose significant challenges for treatment planning. Computational simulation has thus become indispensable for optimizing electrode design and ablation protocols, predicting temperature distribution and coagulation necrosis boundaries, and personalizing treatments through virtual patient-specific modeling. This review provides a comprehensive overview of advancements in RFA simulation methodologies, integrating experimental insights with computational frameworks to advance precision oncology.

Radiofrequency refers to electromagnetic waves with frequencies between audio and infrared ranges, spanning from approximately 104 to 3×1012 Hz. RFA involves the use of unmodulated sinusoidal alternating current (AC) within this frequency range to destroy biological tissues, with a typical frequency of about 500 KHz. This frequency falls in the mid-wave range, high enough (>20 KHz) to induce molecular frictional heating without triggering neuromuscular responses or electrolysis, and low enough (<20 MHz) to limit the energy transfer to a more controllable tissue mass without excessive radiation. It has been shown that alternating currents exceeding 100 mA can cause fatal electric shocks and ventricular fibrillation at the lower frequencies, such as 50 Hz (the frequency of household electricity) [13]. Unlike higher frequency ionizing electromagnetic waves (e.g., typical X-rays at 1018 Hz), radiofrequency energy is non-ionizing and is considered safe for use when applied properly. In the context of RFA, “ablation” can be understood as a virtual surgical ablation, i.e., the inactivation of tissue without removing it from the body, thus producing results similar to those of surgical resection [14, 15].

A typical RFA system consists of a radiofrequency generator, electrode needles, and a grounding plate, which form a complete current circuit with the human liver during the procedure. During RFA, the physician first uses medical imaging to precisely locate the liver tumor. Then, various types of electrode needles (unipolar or multipolar) are inserted into the tumor area [16]. The radiofrequency generator delivers high-frequency current (100-500 KHz) to the cancerous tissue, causing high-frequency vibration and friction of conductive ions and polarized molecules in the tissues around the electrode needles, thus generating Joule heat [17]. Over time, this heat energy is transmitted to the surrounding tissues, causing a coagulation reaction zone around the tumor. As a result, the tumor’s blood supply is cut off, leading to coagulative necrosis of the tumor tissue. The necrotic tissue then peels off and is either absorbed by the body or discharged, achieving tumor destruction [18].

The potential of RFA for liver cancer treatment was first proposed by Rossi et al., with a related study published in 1993 [19, 20]. The effectiveness of RFA in treating liver tumors lies in its ability to exploit the poor heat resistance of tumor cells. Energy deposition into the tumor triggers thermal damage, which produces a tumor-killing effect. RFA involves the flow of alternating current through tissue, causing ionic agitation and impedance heating of the tissue. To establish this current, RFA systems require a closed-loop circuit comprising an electrical energy generator, a needle electrode, the patient (acting as a resistor), and a large-area electrodes (or “grounding pads”). It has been shown that when tissue temperature exceeds 40°C, tumor cells stop dividing; at temperatures above 50°C, tumor cell proteins denature; at temperatures above 60°C, tumor cells coagulate and necrose; and at temperatures reaching 100°C, tissues are charred [21].

Ablation is a very complex procedure, and the success of current tumor RFA treatments depends on several factors, including the structure and materials of the radiofrequency electrode needle, radiofrequency input power, blood perfusion rate, and the conductivity of the liver tissue [22]. **Figure 1** shows the process of RFA for a liver lesion [23].

With the continuous advancement of RFA technology for liver cancer treatment, the electrode needles, as key components, have also undergone significant improvements in clinical practice [24]. Currently, commonly used RFA electrode needles can be categorized based on function and structure. Functionally, they include multi-needle expandable electrode

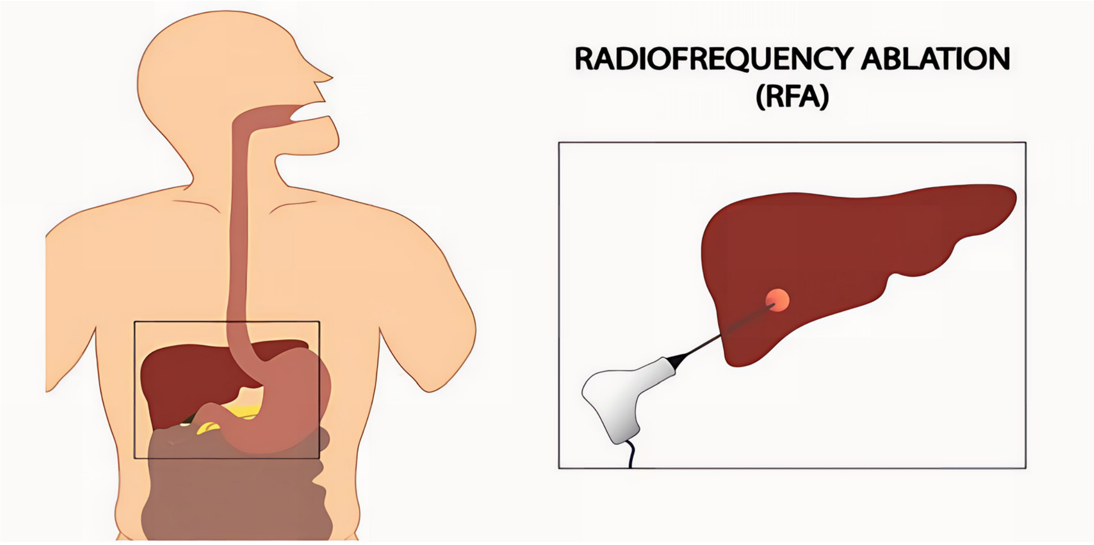

Figure 1. Schematic diagram of radiofrequency ablation. This figure is cited from [23].

needles, internal cooling electrode needles, and perfusion electrode needles. Structurally, they can be classified into unipolar, bipolar, and multipolar needles, depending on the number of needles and subneedles. Among these, multipolar electrode needles can deploy multiple subneedles (typically three or more) at the tip of the needle tube, which are fully expanded in the form of an anchor or umbrella with a uniform spatial structure [25]. A study simulating the performance of spherical and cylindrical electrode tips in cardiac RFA, using a three-dimensional computational model, revealed that the shape of the electrode tip significantly affects the extent of ablation injury, safety, and the risk of complications, providing crucial insights for optimizing catheter design and ablation protocols [26]. Radiofrequency catheter ablation for pulmonary vein isolation is usually achieved by linear point-to-point ablation. However, creating continuous lesions can be time-consuming and requires advanced 3D mapping systems. To overcome these limitations, a multi-electrode ablation system was designed.

Currently, the most commonly used multipolar electrode needles in clinical practice are the multi-needle tip electrode needles developed by MedSphere Technologies [27]. Internal cooling electrode needles can be categorized into liquid-cooled and air-cooled according to the cooling medium. These needles typically feature unipolar or bipolar structures, which reduces tissue temperature around the needle tip by circulating coolant or cooling gas through a built-in hollow cavity. A commonly used internal cooling electrode needle is the Valleylab monopolar needle from Tyco, which is liquid-cooled, with an ablation time of 12 min and an ablation range of up to 3.6 cm in the long axis [28, 29].

In actual RFA procedures, selecting the appropriate electrode needle is crucial for achieving optimal ablation effect, especially considering the size and shape of the tumors. Unipolar and bipolar needles have good therapeutic effects in ablating tumors with a diameter of less than 3 cm. However, due to the small diameter of their needle tubes, these needles often require multiple punctures. Additionally, the temperature distribution around the needle tip is not controllable, potentially causing burning and charring of surrounding tissue, which can cause secondary injuries and increases the risk of complications [30]. The umbrella structure of the multipolar needles allows for a larger ablation range, making them suitable for tumors with a diameter of 3-5 cm. However, their limited output power results in a longer ablation time. Furthermore, fully deploying the multipolar needle may damage adjacent normal tissues, and the tissues in the electrode needle's vicinity are easily burned and charred, limiting their clinical application [31]. **Figure 2** illustrates the schematic diagram of RFA treatment using a multipolar electrode needle [23].

Recent studies have demonstrated that stepwise incremental high-power multi-electrode RFA technology, combined with real-time image guidance, provides a highly effective and safe treatment option for small hepatocellular carcinoma, significantly reducing the rate of local recurrence [32]. However, further validate through multicenter randomized controlled trials is necessary to confirm its long-term efficacy and explore its applicability in a broader patient population.

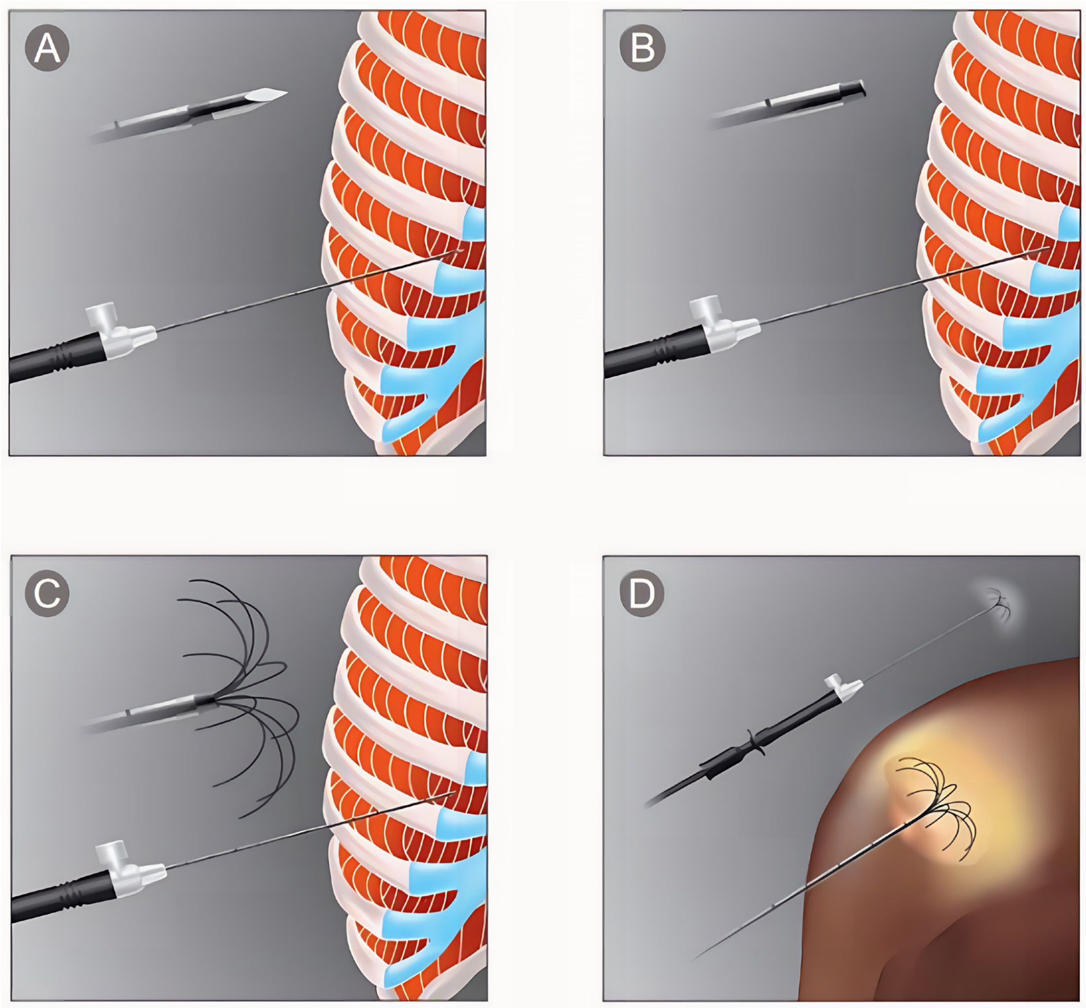

Figure 2. Schematic diagrams of radiofrequency ablation treatment with multipolar electrode needle. (A) a scalpel creates an access route, and the electrode needle is guided toward the liver area in the thoracic - abdominal cavity; (B) the electrode needle is inserted into the targeted liver region under proper guidance; (C) the multipolar electrodes of the needle deploy within the liver, preparing for energy delivery; (D) radiofrequency ablation is carried out, with the electrode acting on the liver lesion to complete the treatment. This figure is cited from [23].

Table 1. Material properties of four electrodes

Electrode Materials	Thermal Conductivity (W/m·K)	Electrical Conductivity (S/m)
Ni-Ti	18	4×10^6
Pt-Ir	71	4×10^6
Au	317	45×10^6
Cu	401	60×10^6

In terms of electrode material selection, Avishek et al. compared the physical properties of four electrode materials (Ni-Ti, Pt-Ir, Au, and Cu) based on numerical modeling, evaluating thermal conductivity and electrical conductivity in the thermal ablation region of a cylindrical liver tissue model (**Table 1**) [33].Despite the theoretical advantages of Au and Cu, the study found that the practical differences in ablation effect between various electrode materials are minimal and have limited clinical significance. When selecting electrodes, it is not necessary to overly focus on the thermophysical properties of the material; factors such as cost and biocompatibility should be prioritized instead.

Biological tissue parameters

Biological tissue parameters refer to the thermophysical properties of liver tissue and its surrounding structures in RFA. These include tissue density, specific heat capacity, thermal conductivity, electrical conductivity, dielectric constant, and blood perfusion rate, among others. These parameters play a crucial role in affecting the ablation temperature field and the extent of thermal damage. Accurate control of these parameters is beneficial for forecasting the ablation temperature distribution, determining the size of the ablation zone, and ensuring the smooth execution of the procedure. Thermal ablation of liver tissue is a complex process, and these parameters are not static; they continuously change with temperature [34]. Moreover, tissue parameters can vary even within different regions of the same tissue [35]. Therefore, it is extremely challenging to measure these parameters simultaneously under non-invasive conditions [36].

Chang et al. used NaCl solution to simulate the liver tissue to measure the temperature-dependent conductivity of the liver [37]. The simulation results showed that liver conductivity exhibited a nonlinear relationship with temperature, largely affecting the final temperature distribution within the tissue. Kröger et al. investigated for the nonlinear variations in tissue parameters with liver tissue temperature and dehydration status, and their simulation results closely matched the actual ablation [34]. Dos et al. used the probabilistic finite element method for the first time to quantify the impact of tissue parameter variations on the ablation damage region of the liver, considering individual and spatial differences [35]. Trujillo et al. observed that the electrical conductivity and permittivity of liver tissue varied linearly at temperatures below 100°C, providing corresponding functional expressions for these relationships [38]. Schutt et al. noted that blood perfusion rate directly affects the heat transfer process during RFA [39]. Their study on the nonlinear changes in blood perfusion rate showed significant differences in ablation outcomes depending on the calculation method used. Johansson et al. incorporated the temperature-dependent changes in thermal conductivity of both normal liver and tumor tissues, representing the conductivity parameters with piecewise expressions [40]. To improve the ablation rate of tumors while minimizing thermal damage to surrounding blood vessels, Fang et al. successfully optimized RFA treatment near vascular structures using a faceted method and computer modeling [41].

These studies underscore the importance of understanding and accurately measuring biological tissue parameters for optimizing RFA treatment protocols. This knowledge is essential for improving treatment efficacy and safety, which requires not only extensive experimental analysis but also robust mathematical modeling.

Biological heat transfer equation

In the study of RFA temperature fields, heat transfer in biological tissues is usually modeled using the biological heat transfer equation. Unlike conventional heat transfer, biological heat transfer is more complex due to the influence of tissue thermophoretic properties, blood perfusion rate, and metabolic activity [42]. This complexity makes the heat transfer process challenging to simulate accurately with a mathematical model, often requiring simplifications and assumptions.

As research into biological heat transfer progresses, various models have been continuously optimized and refined. Currently, four main biological heat transfer models are commonly used: the Pennes biological heat transfer model, the porous medium model, the Weinbaum-Ji-Ji heat transfer model, and the Chen-Holmes heat transfer model [43-46].

• The Pennes biological heat transfer model is based on Fourier’s law of heat conduction and simplifies human forearm tissues into a single cylindrical model. It incorporates blood perfusion rate and metabolic heat production, making it applicable for studying heat transfer in tissues.

• The porous medium model focuses on the heat transfer process between solid and liquid heat phases.

• The Weinbaum-JiJi model primarily focuses on venous heat transfer within muscle tissue, employing a three-layer skin-muscle composite model for more accurate simulations.

• The Chen-Holmes heat transfer model considers the relationship between biological heat transfer and the size and location of blood vessels within the tissues.

Among these models, the Pennes biological heat transfer model takes into account the effects of blood perfusion rate, local arterial blood temperature, and biological metabolic activities. It offers reliable computational results for thermal field simulation closely matching experimental findings. This model is characterized by its simplicity, convenience, and applicability for describing heat transfer process in soft tissues exposed to high temperatures, and it has been widely used in model simulations [47].

During RFA, Wang et al. derived an analytical solution for the blood and tissue temperature distributions, as well as an overall heat exchange correlation in cylindrical coordinates, based on porous medium theory [48]. This was done under local thermal non-equilibrium (LTNE) conditions to better represent the thermal dynamics during RFA. Sheu et al. conducted a 3D thermoelectric analysis of a system consisting of the liver, hepatic artery, and a 4-mm-diameter tumor, focusing on the impact of blood perfusion on heat transfer [49]. Vidya et al. found that closed-form expressions for heat transfer coefficients could accelerate RFA model calculations and identified vessel radius conditions necessary for directional effects on thermal lesions [50]. Tucci et al. developed a biothermal mathematical model based on variable porosity, providing more accurate predictions of the coagulation zone, coagulation diameter, and ablation volume, which can improve medical protocols and device design [51].

Overall, the heat transfer process in biological tissues is complex and difficult to simulate accurately with mathematical models. As numerical models continue to evolve, biological heat transfer equations for RFA will be further refined, aiming to minimize tissue damage and enhance accuracy in treatment protocols.

Evaluation of ablative thermal damage

The evaluation of ablative thermal damage is an important indicator of the effectiveness of RFA. In the process of RFA, tumor cell proteins undergo denaturation, leading to cell necrosis and the formation of a certain range of thermal damage area. Since this process is irreversible, the size (diameter, area, or volume) of the tumor necrotic region serves as the primary metric for thermal damage evaluation. Currently, the commonly used methods for tissue thermal damage assessment include Isothermal Contour method, Arrhenius model, and Thermal Isoeffective Does [52].

The isothermal contour method is the most commonly used quantitative technique in liver tumor RFA simulations. This method involves setting a specific temperature threshold within the ablation temperature field. When the temperature of the ablated tissue exceeds this threshold, it is assumed that the tissue has been thermally damaged by the electrode needle. The isothermal contour corresponding to this threshold serves as the boundary of the ablation thermal damage area. Since protein denaturation and coagulative necrosis of tumor cells typically occur within the temperature range of 50°C-60°C , thresholds of 50°C , 55°C and 60°C are commonly used as evaluation benchmarks for treatment [53]. The equation for the isotherm threshold method is:

$$V = \iiint_{\Omega} \mathrm{dv} \ (\Omega \geq \mathrm{T}^{\circ}\mathrm{C}) \tag{1}$$

Where V represents volume of the ablated tissue, Ω represents the tissue region affected by thermal damage, and T is the temperature threshold.

Thermal Isoeffective Dose is a standardized metric used to quantify tissue damage in thermal therapies (e.g., radiofrequency ablation, microwave ablation). Its core concept is to compare the effectiveness of different treatment regimens by mathematically converting varying temperature-time exposures into an equivalent dose value. In clinical practice, the commonly used thermal dose unit is CEM43 (Cumulative Equivalent Minutes at 43°C), which indicates the equivalence of the actual temperature-time curve to the exposure time at 43°C [54]:

$$\mathrm{CEM43} = \sum_t R^{(43-T(t))} \cdot \Delta t \tag{2}$$

Where, t represents time, R= 0.5 (T>43°C) or R=0.25 (T<43°C), T means the thermodynamic temperature (K) at time t.

The Arrhenius model is a mathematical model derived from chemical reaction kinetics, commonly used to quantify tissue damage during thermotherapy or thermal ablation (e.g., radiofrequency ablation, microwave ablation). The core concept is that tissue damage is exponentially related to both temperature and time, with the probability of cell necrosis being predicted by integrating the effects of temperature and time [50]. The damage index (Ω) in the Arrhenius model is calculated as follows:

$$\Omega(\mathrm{t}) = \int_0^{\mathrm{t}} A \cdot e^{-\frac{Ea}{R \cdot T(\tau)}} \cdot \mathrm{d}\tau \tag{3}$$

Where A represents the frequency, Ea is the activation energy, R is the universal gas constant, and T (τ) is the temperature at time τ.

With the development of computer technology, the future direction of ablation thermal injury evaluation will focus on multimodal real-time assessment (combining impedance monitoring, temperature imaging, and artificial intelligence algorithms), dynamic tissue parameter correction (integrating individual differences such as blood perfusion and conductivity), and precise ablation boundary-defining techniques (e.g., elastography, high-resolution imaging), to enhance the personalized efficacy assessment and improve the precision of intraoperative modulation.

RFA temperature field simulation

The computational modeling of liver thermal ablation is primarily based on the Pennes equation, integrated with numerical methods such as finite element method and finite surface method, along with tissue damage models [55]. With the continuous development of computer technology and numerical computation, reconstructing a three-dimensional model of bioheat transfer using finite element modeling software has become a standard approach. This allows for finite element simulation and analysis to simulate the distribution of the temperature field during RFA. The utilization of finite element method greatly simplifies the complexity of controlling the temperature distribution in RFA and enhances the ability to predict the ablation region.

In the finite element simulation of RFA, several studies have contributed valuable insights. Ooi et al. established a three-dimensional impedance finite element model of RFA, focused on the dynamics of ablation temperature field, thermal damage area, and input voltage under different electro-thermal boundary conditions [56]. Chen et al. investigated the effects of variations in vessel size, horizontal distance between vessels, and the positioning of ablation electrode needles on the ablation temperature field through a three-dimensional simulation model of RFA that incorporated blood vessels [57]. Goldberg et al. coupled the radiofrequency electric field with the heat conduction process in their simulation of liver tissue during RFA [28]. Their study successfully predicted the temperature distribution within the liver during the ablation process, yielding ideal results that matched clinical outcomes. Lee et al. focused on a “claw-shaped” radiofrequency ablation electrode [58]. Their finite element simulation demonstrated that this electrode design effectively expanded the ablation range. Since then, finite element simulation has been widely used in the prediction of temperature field in RFA procedures.

Discussion

RFA has emerged as the cornerstone in the treatment of hepatocellular carcinoma, offering a minimally invasive, safe, and effective alternative to traditional surgical methods. This review synthesizes the technical principles, critical components (including electrode needle typology and materials), dynamic behavior of biological tissue parameters, bioheat transfer modeling approaches, and thermal damage assessment methodologies pertinent to RFA. Our analysis highlights the significant advancements made in this field, while also acknowledging the persistent challenges that remain.

Selection of electrode needles is a critical determinant of RFA therapeutic efficacy. Electrode needles are broadly classified as unipolar, bipolar, or multipolar configurations. The choice of electrode is influenced by tumor characteristics, including morphology and size. Unipolar and bipolar systems demonstrate high efficacy for tumors <3 cm in diameter, whereas multipolar electrodes are frequently employed for larger lesions (>3 cm) to achieve an expanded ablation volume in a single session. While computational simulations suggest that materials with high thermal conductivity (e.g., Cu, 401 W/m·K) or high electrical conductivity (e.g., Au, 45 $*10^6$ S/m) could theoretically enlarge the ablation zone, empirical validation has shown that material selection has only a negligible impact on the ablation volume, with differences of less than 0.1% observed in clinical settings. Consequently, clinical electrode material selection should prioritize biocompatibility, cost-effectiveness, and device engineering considerations over the pursuit of marginal thermophysical property optimization.

Thermal ablation of hepatic tissue is an intricate biophysical process influenced by several dynamic parameters. Notably, tissue thermal conductivity, electrical conductivity, and blood perfusion rate exhibit significant spatiotemporal variations, which are dependent on factors such as temperature and anatomical location. These variations directly influence the distribution of the resulting ablation temperature field. Although contemporary research employs nonlinear modeling frameworks (e.g., probabilistic finite element methods) to partially mitigate parameter uncertainty, the absence of non-invasive, real-time measurement techniques remains a fundamental bottleneck constraining the accurate prediction of ablation margins. Ongoing refinement of numerical systems and the bioheat transfer equations governing RFA is imperative to enhance predictive accuracy and minimize collateral tissue damage.

Bioheat transfer modeling for RFA predominantly utilizes four principal frameworks: the Pennes bioheat transfer model, the porous medium model, the Weinbaum-Jiji model, and the Chen-Holmes model. Among these, the Pennes model, valued for its computational efficiency and relative simplicity, remains the most widely adopted in RFA simulations for hepatic malignancies. The integration of numerical methods, such as finite element method and finite surface method, with tissue damage models allows for the creation of three-dimensional biothermal simulations using finite element software. Subsequent finite element simulation of the RFA temperature field distribution constitutes the prevailing methodological paradigm. Notably, advanced models, such as the porous medium and variable porosity approaches, enhance the physiological accuracy of these simulations. For thermal damage assessment, the isothermal threshold method and the Arrhenius integral model represent established standards; however, their intraoperative precision is significantly improved by integrating multimodal real-time monitoring techniques, such as impedance feedback and artificial intelligence-driven dynamic correction algorithms.

Conclusions

Optimizing RFA technology necessitates a multidisciplinary approach focused on three critical domains: the advancement of smart electrode systems incorporating shape-adaptive designs, the integration of individualized tissue parameter databases to better reflect patient-specific tissue properties, and the strategic exploration of multi-energy ablation techniques, such as RFA- microwave ablation synergy to broaden therapeutic indications. Crucially, achieving a paradigm shift from empirically guided interventions toward predictive precision requires rigorous large-scale clinical validation coupled with iterative refinement of computational models. Successfully implementing this “accurate prediction” framework holds significant potential to substantially improve long-term survival outcomes and quality of life for patients with hepatocellular carcinoma.

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