Chapter 1
Physics and Physiology of Thermal Ablations

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Thermal Ablation

Thermal ablation of tumor occurs with either extreme high or low temperatures. The desired result, irreversible cellular injury, results in coagulative necrosis. Coagulative necrosis may result from many conditions including extreme temperatures, ischemia, or hypoxia, and is characterized by short-term preservation of the architecture of the necrotic tissue, as the injury which results in necrosis also destroys intrinsic mechanisms for breakdown of cellular material. Coagulative necrosis is seen throughout the body and contrasts with liquefactive necrosis, which is characteristic in the central nervous system. Hypothermic injury leading to coagulative necrosis occurs with cryoablation (CA). Hyperthermic injury leading to coagulative necrosis occurs with radiofrequency ablation (RFA), microwave ablation (MWA), high-intensity focused ultrasound, and laser ablation (Fig. 1.1 and Table 1.1).

Heat-ablated lesions have been characterized as having three zones: the central zone in which ablation-induced coagulative necrosis occurs; a peripheral zone of sub-lethal hyperthermia in which cells may undergo apoptosis or may recover; and a surrounding zone of unaffected tissue [1]. Direct cellular damage depends upon the thermal energy applied, the rate of energy application, and the sensitivity of the target tissue. Mitochondrial dysfunction and inhibition of DNA replication are

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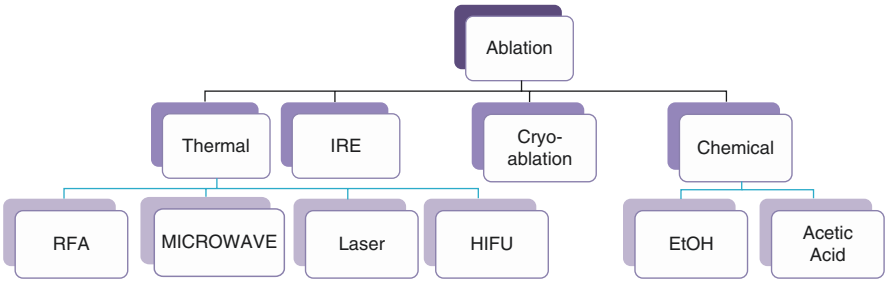

Fig. 1.1 Ablation modalities. In general, ablation modalities can be subdivided into thermal and non-thermal. Thermal modalities depend on increasing temperature to effect tissue necrosis and they include RFA, microwave ablation, laser ablation and high-frequency ultrasound ablation (HIFU). Non-thermal ablation modalities include: cryoablation, chemical ablation, and irreversible electroporation (IRE). Chemical ablation (acetic acid and alcohol ablation) has fallen out of favor in the USA. Despite being inexpensive, its efficacy is unpredictable and requires repeated procedures to approach the efficacy of other ablative modalities. HIFU and IRE are still in an investigational stage and their applicability is limited. Cryoablation and microwave ablation are becoming the most commonly utilized tumor ablative modalities in the USA

Table 1.1 Comparison of ablative modalities

	Cost	Experience	Ease of use	Outcomes
RFA	+	++++	++++	++
MWA	++	++++	++++	++++
Cryoablation	+++	+++	+++	++++
IRE	++++	+	+	++

Even though most published experience is with RFA, it has fallen out of favor because MWA and cryoablation have been shown to have superior outcomes. Cryoablation, though costlier than thermal ablative modalities, has shown better outcomes for renal cell carcinoma and for pain palliation. Cryoablation's advantages include visibility and uniformity of ablation zone (Fig. 1.7). IRE data are lacking, which coupled with its cumbersome technique and high cost has limited its applicability.

well-correlated with hyperthermic injury, ultimately resulting in changes to cell membrane integrity and cell death [1].

Complete destruction by thermal ablation requires that the entire tumor and an ablative margin be subjected to cytotoxic temperatures [2]. The ability to heat or cool large volumes of tissue in different environments is dependent upon the energy deposited, local tissue interactions, and energy lost before inducing thermal damage [2].

Radiofrequency Ablation

Physics

Radiofrequency ablation is based upon the application of alternating electric current which is delivered to the target tissue between electrode(s) resulting in frictional tissue heating and ultimately coagulative necrosis.

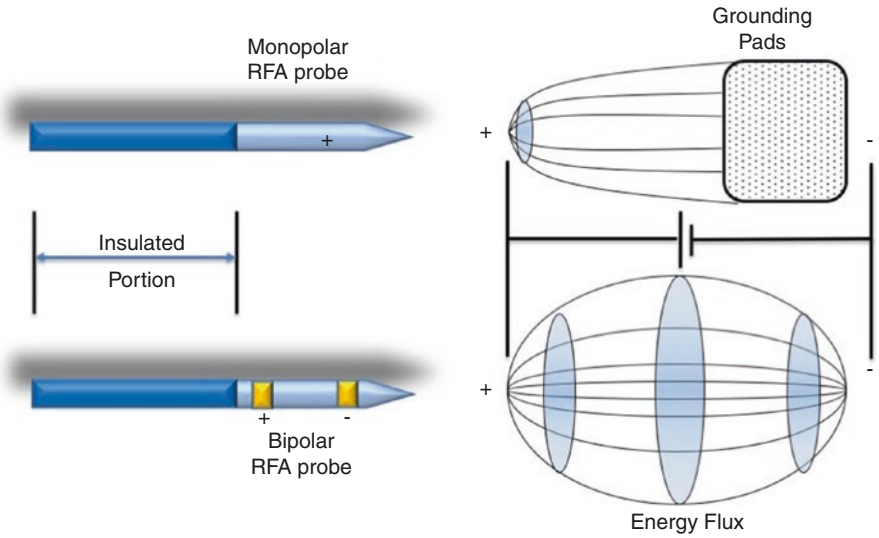

Fig. 1.2 RFA system design: In a monopolar (upper) RFA system, the alternating electric current travels within the patient between the RFA electrode (cathode) and the grounding pad (anode). At the probe tip energy flux is very high as the cross sectional area it traverses is small, resulting in energy deposition. The same amount of energy is dispersed over a larger area reducing the energy flux, on the pad side. In a bipolar (lower) RFA system, the electric current travels within the patient between two or more electrodes which function as both anode and cathode. No grounding pads are necessary

Radiofrequency (RF) energy is part of the electromagnetic spectrum, spanning frequencies from 3 Hz to 300 GHz. The RF ablation electrodes are part of an electrical circuit which when closed results in energy deposition in the form of heat (ablation) in the target tissue. RFA systems may be monopolar or bipolar in design (Fig. 1.2). Within the electrical circuit of a monopolar system, the RFA electrode acts as the cathode. Dispersing/grounding pads, which are typically applied to the patient's thighs, close the circuit and function as the anode. In the monopolar system, the RF current travels from the system generator to the ablation electrode in the tumor, through body tissues to the grounding pads on the skin, and then back to the generator. The area of the RFA electrode is quite small and creates high energy flux. Conversely, the large area of the dispersing/grounding pads minimizes energy flux. Therefore, within this circuit, tissue damage is limited to the area with high energy flux surrounding the ablation electrode, and tissue damage is avoided at the grounding pads when properly applied.

Bipolar RFA systems, which are less common in clinical RFA, utilize two or more bipolar ablation electrodes which are placed into the tumor. The applied RF current runs between the ablation electrodes without the need for grounding pads. Each electrode in bipolar systems contains high energy flux. By eliminating dispersing pads, bipolar RF systems minimize energy loss and more efficiently create greater ablation volumes without risking skin burns.

The mechanism of heating with RF ablation occurs through rapid realignment of molecules adjacent to the RF electrode as an alternating current is applied to the circuit. Dipolar molecules within the target tissue, which are predominantly water

molecules, attempt to align with the current. As the direction of the current rapidly alternates, the dipolar molecules rapidly realign with the current resulting in vibration and frictional heating. The frictional heating resulting from dipolar molecule realignment causes high temperatures within the tissues immediately adjacent to the electrode. These high temperatures, resulting from frictional heating, are then thermally conducted to the adjacent tissue.

Ohm's law, *current* = *voltage*/*resistance*, assists with understanding RFA. RFA is dependent upon the flow of current within the circuit. However, RFA is adversely impacted by increased resistance to flow within the circuit, known as impedance. The significance of impedance is further understood when assessing the power of a system, *Power* = *voltage* × *current*. When substituting into this equation using Ohm's law, $Power = voltage^2/resistance$, the inverse relationship of power and resistance is noted. Several methods to decrease impedance have been employed in RFA systems: these include the expansion of electrode surface area, such as with multi-tine electrodes, which increases heat distribution within the target tissue and decreases the occurrence of charring; pulsing the power input of a system which allows brief termination of power input to an electrode when a rapid increase in impedance is detected, allowing the tissue to cool, thereby decreasing charring; internal cooling of the electrode to eliminate charring at the electrode-tissue interface; and injection of saline into the ablation zone to increase conduction of electricity into the target tissues. Any source of impedance, or resistance to flow, within the circuit limits the efficacy of RFA. Tissue desiccation occurs when too much energy is deposited in a target tissue too rapidly. The water vapor and tissue charring associated with desiccation insulate the electrode, limiting current flow, which limits further tissue ablation (Fig. 1.3).

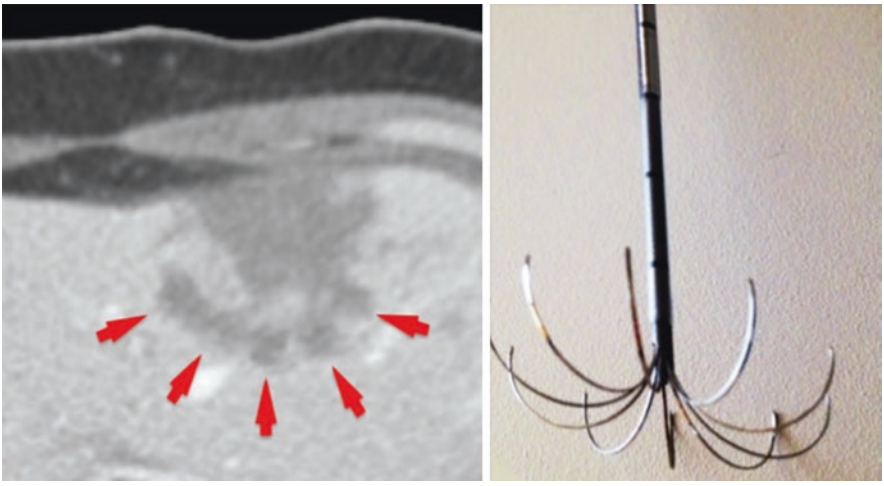

Fig. 1.3 Effect of time on ablation efficacy. Contrary to MWA, RFA relies on a closed electrical circuit and a continuously flowing electrical current to deposit energy in the tissue. If the initial power is set too high (as in this example using an umbrella probe – right), the resulting initial high energy deposition chares the tissue surrounding the RFA tines (red arrows). The dehydrated tissue ceases to be a conductor and the circuit opens. This prevents further deposition of energy and limits the efficacy of RFA and the size of the ablation zone

Physiology

Body tissues are sensitive to temperature change. Tissue death occurs within 2 seconds at 55 °C and is instantaneous at 100 °C [3]. Ideal RFA occurs when target tissues are heated to the range of 60–70 °C for several minutes in a controlled manner, resulting in coagulative necrosis without charring or vaporization. When temperatures exceed 100 °C, undesirable tissue changes occur, including boiling, vaporization, and charring, all of which result in increased impedance, directly decreasing energy transmission through the circuit and limiting the ablation zone. To maximize the RF ablation zone, energy deposition in RFA should be slow and controlled.

Inhomogeneity within tissues results in variable energy conduction. This variable energy conduction results in significant inhomogeneity in heating within the RFA zone. The energy conducted through the local tissues is also adversely affected by temperature losses that occur with flowing blood in the ablation zone, known as "heat sink". Temperature losses are encountered when a blood vessel 3 mm or greater in diameter is in the region of the target lesion. Flowing blood leads to relative cooling of tissues along a vessel in the ablation zone, counteracting the thermal conduction of heat from the tissues surrounding RF ablation device. The "heat sink" effect increases the likelihood of residual viable tumor near the vessel wall and increases the likelihood of local tumor progression.

Within the peripheral RFA zone of sub-lethal hyperthermia, inflammatory infiltrates specific to the ablated tissue have been reported [1]. Following RFA, immune activation has been demonstrated within the ablation zone as well as within untreated tumors and in the peripheral bloodstream [1]. The release of intracellular material as well as components from the disrupted extracellular tissues results in activation of immune response and pro-inflammatory cytokines within hours to days after RFA [1].

Microwave Ablation

Physics

Microwave ablation is based upon the generation of an oscillating electromagnetic field resulting in continuous realignment of polar water molecules in the ablation zone which causes frictional tissue heating and ultimately coagulative necrosis.

Microwave electromagnetic energy ranges from 300 MHz to 300 GHz. Clinically used microwave ablation devices typically operate between 915 MHz and 2.5 GHz [1, 2]. Following placement and activation of a microwave ablation antenna, molecules which possess an intrinsic dipole moment (primarily water) begin to continuously realign in response to the oscillating electromagnetic field (Fig. 1.4). The phenomenon of energy loss as rotating dipoles cannot keep up with the alternating magnetic field is known as dielectric hysteresis. The increased kinetic energy generated by the rotation of these molecules leads to tissue heating. The ablation zone

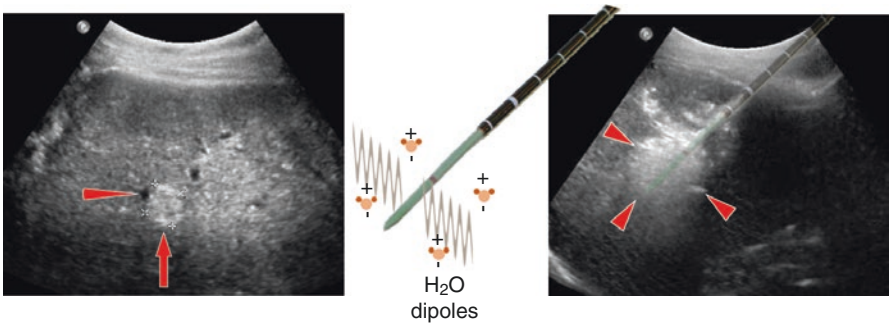

Fig. 1.4 Microwave ablation. The image on the left shows a 1.5 cm colon metastasis to the liver (red arrow) abutting a blood vessel (red arrowhead). The microwave antenna generates an oscillating electromagnetic field resulting in oscillation of dipole molecules (predominantly water). The phenomenon known as dielectric hysteresis leads to energy deposition and tissue heating. The electromagnetic field penetrates all biological tissues and can generate heat rapidly, with the potential to overcome heat sink and charred tissue. The image on the right is during ablation and shows the target lesion obscured by a large gas containing ablation zone (red arrowheads). The heat sink from the vessel (no longer seen) noted in the first image failed to limit the ablation zone

generated with MWA is not dependent upon electrical conductivity nor subject to impedance, but rather permeates all biological tissues. Without concern for tissue desiccation or charring, MWA is capable of producing larger and hotter ablation zones at a more rapid rate when compared to RFA. As MWA utilizes an electromagnetic field and not a circuit, grounding pads are not required.

Microwave ablation zones are dependent upon the number, design, and orientation of antenna, upon the power applied and upon the microwave frequency. The antennae provide energy transfer from the system into the target tissue. There are many MWA antenna designs, and designs often involve trade-offs in efficiency, size, and heating pattern [2]. At certain microwave frequencies, tissues may be actively heated up to 2 cm away from the antenna, which contrasts with the active zone of heating with RFA which is limited to a few millimeters around the ablation electrode [1]. Multiple antennae may be used simultaneously with MWA. With constructive phasing of the electromagnetic fields, the generated heat is proportional to the square of the number of antennae, working synergistically to increase the size of the ablation zone [1].

Physiology

Coagulative necrosis characterizes cell death in MWA, as in the other thermal ablation modalities. Temperatures with MWA can exceed 150 °C. Such temperatures are instantly lethal to biological tissues. The rapid and high temperatures that occur with MWA result in extensive vaporization and charring of ablated tissues, which in contrast to RFA do not adversely impact ablation and yield more consistent ablation

results across all tissue types [4]. The large volume of MWA zones, coupled with rapid generation of high temperatures, makes MWA less susceptible to heat sink effect and results in shorter ablation times when compared to RFA.

MWA is considered a weak stimulator of local inflammation and immunogenicity when compared to other ablation modalities, with minimal induction of pro-inflammatory cytokines [1]. Despite this, a statistically significant correlation between survival outcomes and extent of immunocyte infiltration has been demonstrated with MWA [5].

Cryoablation

Physics

Cryoablation is based upon the circulation of a cryogen, a gas that cools as it expands, into a cryoprobe resulting in creation of ice, with resultant coagulative necrosis of the target tissue. The phenomenon is called the Joule-Thomson effect.

As the cryogen gas passes from a region of high pressure to low pressure within the device (no gas is released in the patient), whether through a valve or into an expansion chamber, rapid cooling of the cryoprobe to −160 °C or colder occurs [4]. This rapid cooling results in freezing and creation of an ice ball surrounding the cryoprobe (Fig. 1.5). After the initial formation of ice within the tissue along the cryoprobe, passive thermal diffusion results in growth of the ice ball.

Cryogenic liquids have boiling points less than −150 °C. Liquid nitrogen has the greatest freezing capacity of liquid cryogens but cannot be used in devices with a diameter less than 3 mm [6]. In contrast, Argon is safely used in small diameter percutaneous devices and therefore is the cryogen mostly used for clinical cryoablation.

The surface area of a cryoprobe is proportional to its cooling capacity, with larger cryoprobe diameters resulting in greater size of ablation zones. Multiple cryoprobes are generally required to treat a target tumor percutaneously. In addition to creation of a larger ice ball and cryoablation zone, the use of multiple cryoprobes creates a more uniform zone of lethal ablation and lower ablative temperatures in the targeted tissue [6].

Inhomogeneity within target tissues may result in variable expansion of the ablation zone and growth of the ice ball. Cryoablation is challenged by loss of intended freezing temperature changes in the presence of nearby large blood vessels. Flowing blood leads to relative warming of tissues along vessels in the cryoablation zone, counteracting the removal of energy from the tissues by the cryoprobe. As with the “heat sink” effect seen with RFA, this increases the likelihood of residual viable tumor near the vessel wall and increases the likelihood of local tumor progression. Being the opposite of a heat sink effect, this is properly termed the heat-pump effect.

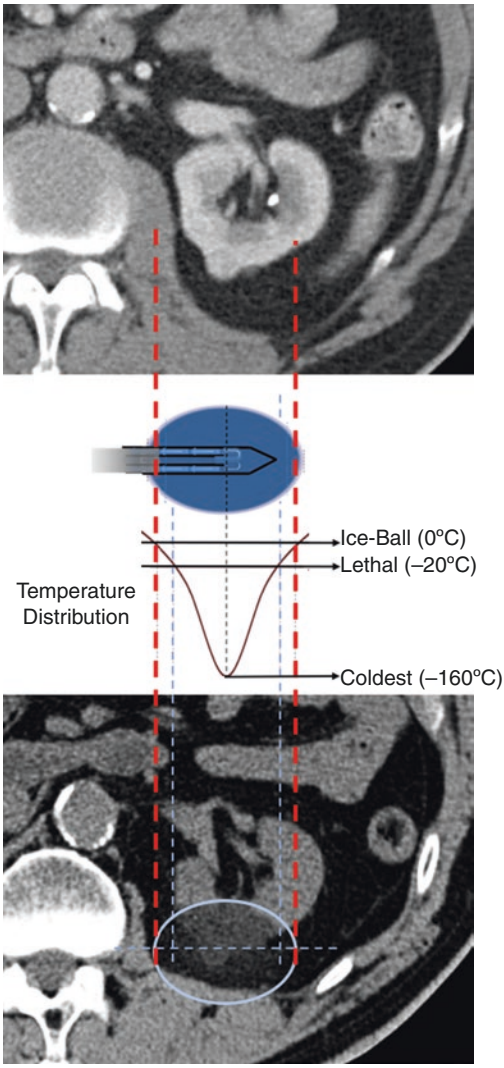

Fig. 1.5 Cryoablation. The top image shows a small exophytic RCC in the posterior aspect of the left kidney. As Argon (a cryogen) passes from a region of high pressure to low pressure within the device (middle image), whether through a valve or into an expansion chamber, rapid cooling of the cryoprobe to −160 °C or colder occurs via the Joule-Thomson effect. This results in the creation of an ice ball surrounding the cryoprobe. The only visible isotherm is the ice ball itself at 0 °C (dashed red lines). The lethal isotherm (~ −20 °C) is 2–5 mm deep to the visible ice ball (dashed blue lines)

Physiology

Tissue response to cryoablation depends upon the severity of freezing within the tissue. Various biological responses have been described with cryoablation and are dependent upon the temperature within that portion of the ablation zone. Severe freezing injury, as occurs with "lethal ice", is the objective of cryoablation. Direct cellular injury occurs when extracellular water freezes before intracellular water, resulting in an osmotic gradient with fluid flux from the cell to the extracellular space, causing cell dehydration. This dehydration results in distortion of the plasma

membrane [1]. Intracellular freezing results in direct cell membrane and organelle injury, leading to loss of homeostasis and further cell desiccation. Ice crystals from cellular freezing cause mechanical injury via shearing forces [6]. With thaw of the ice ball, the hypertonic intracellular compartment experiences an exaggerated fluid shift which results in cell membrane rupture [1]. In the central zone near the cryoprobe, uniform cell death is characteristic.

A zone of non-lethal ice is present toward the periphery of the ice ball, where the tissue temperatures are 0 to −20 °C. In this region, some cells are killed while others survive. Apoptosis may be seen within this portion of the cryoablation zone, where temperatures are insufficient to uniformly kill all cells. Tissue injury related to non-lethal ice may trigger apoptosis up to several days after ablation [6].

Cryoablation is dependent upon implementation of sequential freeze-thaw cycles, and each component of the freeze-thaw cycle (such as the cooling rate, the warming rate, and the temperature produced) contributes to injury to the target tissues [6]. The fastest cooling rate is desired, as faster freezing to lower temperatures results in the formation of lethal intracellular ice crystals. Cells die in progressively greater numbers as the temperature falls from −5 °C to −50 °C. With the treatment of cancer, the goal is to obtain the coldest lethal ice possible throughout the target area and within a volume of tissue around the tumor to ensure death of all cancer cells. While extensive tissue damage occurs at −20 °C to −30 °C, cancer cell destruction may be incomplete [6]. Duration of freezing with cryoablation varies and is partially determined by growth of the ice ball. Ideally, tissues should be kept in the frozen state for 5 minutes or longer to produce solute effects, ice-crystal formation, and recrystallization effects [6].

Slow, passive thawing of the frozen tissue is a major destructive factor. With a longer duration of thaw, greater damage to cells occurs, including increased solute effects, ice-crystal restructuring, prolonged oxidative stress, and growth of ice crystals [6]. Vasoconstriction and vascular injury which occur in response to cryoablation are prolonged with a longer, passive thaw. This allows further destructive changes to occur within the ablation zone. Providing a delay after thawing, before initiating the second freeze cycle, results in ongoing tissue hypothermia and oxidative stress [6]. Rapid thawing increases the chance of cell survival and should be avoided.

Repeating the freeze-thaw cycle produces faster and more extensive tissue cooling, resulting in an increased volume of frozen tissue which is seen as a larger ice ball. By repeating the freeze-thaw cycle, the margin of lethal ablation is moved closer to the outer limit of the frozen volume [6]. The use of temperature sensors, mounted in needles, enables accurate assessment of temperatures within the ice ball. This specific temperature information is useful both for ensuring adequacy of lethal ice covering target tissues and for protecting adjacent non-target tissues.

In contrast to RFA and MWA, cryoablation does not result in denaturation of proteins. These tumor antigens are preserved and released upon tumor thawing and reperfusion, resulting in a robust inflammatory response and the potential to stimulate an immune response. Cryoablation has been shown to produce antibodies to

ablated tumor antigens in both animals and humans [7]. After cryoablation, pro-inflammatory cytokines are released in higher quantities than after RFA or MWA. The systemic response to the release of recognizable intracellular contents following cryoablation of hepatocytes may lead to the rare phenomenon of cryoshock. Kupffer cells are stimulated to release pro-inflammatory mediators that may result in systemic inflammatory response syndrome, disseminated intravascular coagulopathy, multi-system organ failure, and death [1]. Cryoshock is most severe when at least 35% of the liver has been cryoablated. In addition to a robust stimulatory effect on the immune system, cryoablation may also result in an immunosuppressive effect which has been attributed to the balance between necrosis and apoptosis [1]. Apoptosis does not result in release of intracellular contents as seen with necrosis, and may result in immunosuppression toward apoptotic cell antigens [1]. Whether necrosis or apoptosis will exert more effect on the inflammatory and immune responses following cryoablation is not readily predicted, and may be influenced by factors related to ablation, tumor type, and the individual [1].

Non-thermal Ablation

Irreversible Electroporation (IRE)

Non-thermal ablation occurs with electroporation, in which electrical pulses applied induce permeabilization of the cell membrane. Irreversible electroporation (IRE) is a non-thermal ablation technique that permanently creates nanoscale defects in the cell membrane by exposing cells to short and intense electric fields [8]. The altered intracellular environment ultimately induces cell death via both apoptosis and coagulative necrosis [9]. Electroporation can ablate significant volumes of tissue without producing a thermal effect, thereby preventing damage to surrounding structures. IRE planning uses mathematical modeling to precisely predict the treated area and allows for accurately delineated ablation zones [8]. In contrast to thermal ablation (RFA and MWA), the nonthermal nature of IRE makes it forgiving to extracellular matrix and organ architecture, thereby allowing for treatment of complex lesions that are unapproachable with thermal techniques.

Physics

Electroporation generates a destabilizing electric potential across cell membranes that leads to the creation of nanoscale defects in the lipid bilayer [10]. In IRE, these defects are non-transient and lead to cell death. Contact electrodes are used to apply short (microsecond to millisecond) high voltage pulses to cells or tissues, permeabilizing the cell membrane (Fig. 1.6) [10].

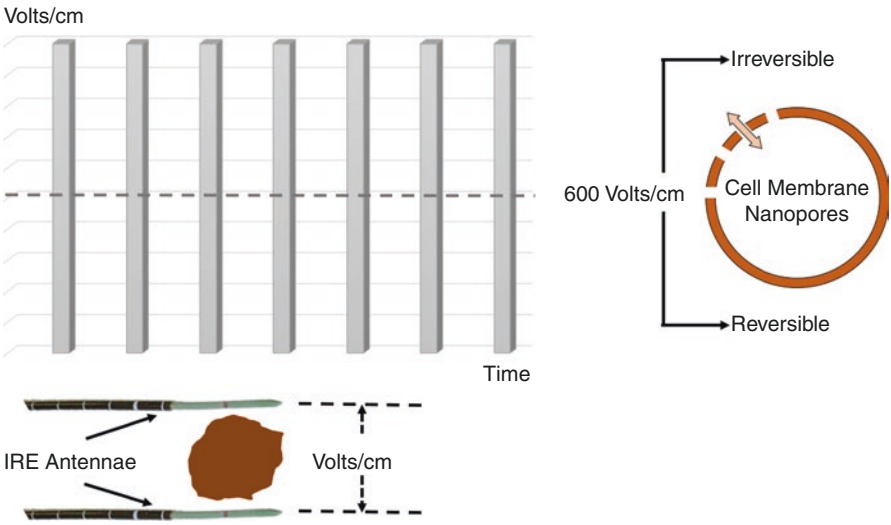

Fig. 1.6 Irreversible electroporation. IRE probes are placed parallel within or spanning the target tissue to ensure a uniform ablation zone. A series of high-voltage, microsecond electrical pulses are delivered through the probes to the target tissue. The physiological effect is the creation of small membrane pores in the affected cells. When the voltage gradient between the IRE antennae is below 600 Volts/cm, the nanopores heal spontaneously after cessation of the voltage and transmembrane homeostasis is re-established. When the voltage gradient between the IRE antennae is above 600 Volts/cm, these nanopores are generally irreversible. The subsequent permanent loss of cell homeostasis results in cell death

An IRE device has three components: the generator, monopolar probes, and a cardiac syncing device. The generator is interfaced with a computer system with treatment planning software [11]. The generator delivers low-voltage, high-energy current through monopolar probes connected to the generator. The system can connect up to six monopolar needle electrodes and the electrical pulse is delivered between two probes at a time. The treatment planning software helps determine the number of probes required to create the desired ablation zone.

Voltage, pulse frequency, pulse duration, electrode number, and electrode spacing are parameters that are entered into the IRE console, which then generates a two-dimensional representation of the ablation shape, perpendicular to the direction of the needle electrode insertion [11]. Ongoing research in this area is underway, but the most important parameters affecting the ablation zone are impedance distribution, pulse characteristics, and electrode configuration (size, spacing, and number) [12]. Currently, the most common practiced settings for tumor ablation are voltage 1500 V/cm, 70–90 pulses of 70–90 μs, electrode spacing of 1.5–2 cm, and active electrode tip length of 1–1.5 cm [11].

The monopolar probes are 15–20 cm length, 19-gauge needles with 1 cm depth markings along the shaft of the probe. The active tip can be exposed between 1 and 4 cm, depending on the desired size of the ablation zone and the depth of the lesion.

The needles are placed under ultrasound guidance, and therefore the exposed electrode surface is echogenic. Parallel insertion of the probes is important, as is avoiding convergence or divergence of the probes, which can result in a nonuniform ablation zone. The ideal spacing between probes is 1.5 and 2 cm. Inaccurate spacing increases the chances of high current errors.

Early experiences resulted in transient arrhythmia in human subjects undergoing IRE and therefore the generator also incorporates a five-lead system which synchronizes pulse delivery with the patient's electrocardiogram (ECG). When an electrical energy pulse is delivered, this system detects the rising slope of the R-wave and sends a signal to the generator [11].

Physiology

Electroporation increases the permeability of the cell membrane as it exposes the cell to an electrical pulse [13]. This produces disruption of the lipid bilayers of the cell membrane on which nano-pores are formed allowing normally impermeant matter to diffuse freely through the membrane [10, 13]. A combination of studies showed that as electric potential across the cell membrane increases due to the pulse delivered, the cell membrane can either be permeabilized reversibly (does not induce cell death) or irreversibly (which would lead to necrosis and death). This mechanism of permeabilization of the cell membrane with electrical pulses is not fully understood. However, the outcome depends on the pulse amplitude and duration of number of pulses [10]. Unlike thermal ablation, the cell membrane's permeabilizing electric filed is unaffected by local blood flow and thus allows for control over the extent of the affected tissue.

The external electric field delivered is the main parameter that affects the transmembrane potential——the potential difference across the plasma membrane [13]. Intra- and extracellular solute transport is highly regulated by the lipid bilayer membrane. This creates a density difference between the intra- and extracellular space, resulting in a voltage potential difference across the membrane. The electric field provides a local driving force that propels larger or polar molecules and ions, which the membrane would normally be impermeable to, into the cell [13]. When this transmembrane potential reaches a specific threshold, electroporation occurs and the plasma membrane undergoes structural rearrangement. Once the nanoscale pores are created in the membrane, the cell requires increasing energy to preserve its transmembrane ionic differences. If the adenosine triphosphate-dependent protein pumps are unable to compensate for the diffusion differences, this altered intracellular environment that IRE has created will induce cell death via apoptosis and coagulative necrosis [13] (Fig. 1.7).

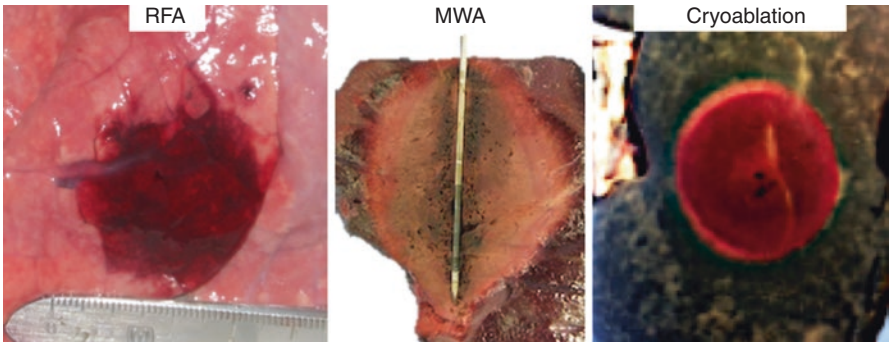

Fig. 1.7 Ablation zone comparison between ablation modalities. RFA ablation zone shows the highest border irregularity which contributes to lower response rates. Consequently, a wider ablation margin is recommended for RFA, up to 10 mm. MWA shows a relatively smoother ablation boundary whereas cryoablation is characterized by a near-spherical and uniform ablation zone

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