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Irreversible electroporation and thermal ablation of tumors in the liver, lung, kidney and bone: What are the differences?

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Abstract Focal treatment with radiofrequency, microwave and cryoablation has been increasingly used for the treatment of tumors in patients who cannot undergo surgical resection and in select patients with early stage or oligometastatic disease. Each of these ablation modalities has a unique working principle and biophysics underlying the ablative effect, which largely determines the clinical indication for its application. Irreversible electroporation, a relatively new ablation technique with a predominantly nonthermal cell killing mechanism has emerged as an alternative treatment technique for tumors that are contraindicated for thermal ablation because of safety or efficacy considerations. Here, established thermal ablation techniques are compared with irreversible electroporation for treatment of tumors in the lung, liver, kidney and bone, and rationale is provided to guide selection of the most appropriate technique for each clinical setting.

A substantial number of patients have tumors that cannot be safely resected through surgery because of unfavorable tumor location, presence of multifocal disease or patient comorbidities [1,2]. Image-guided tumor ablation with radiofrequency (RFA), microwave ablation (MWA) or cryoablation has been developed as an alternative to surgical resection for these patients. These ablation techniques rely on sustained alterations of tissue temperature for cytotoxic effect and have been reported to be highly effective for the treatment of both primary and metastatic disease [2—7]. However, the working mechanisms of these techniques contraindicate their use in patients with tumors that

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are adjacent to major blood vessels, bile ducts, large airways, nerves, digestive or urinary tract because of safety or efficacy concerns. Ablation with irreversible electroporation (IRE) has been recently assessed for the safe and efficacious treatment of tumors that cannot be treated with thermal ablation techniques. As a relatively new technique, there is limited clinical experience with IRE and therefore the risks and benefits of using this technique have not been completely defined.

The purpose of this article was to compare IRE with thermal ablation techniques while contrasting the respective working mechanisms as well as techniques and outcomes in clinical practice in order to provide a rationale for clinicians to select the most appropriate technique for varying situations.

Biophysical considerations

Hyperthermic ablation

RFA and MWA are heat-based techniques that deliver electrical or electromagnetic energy into target tissue by using needle mounted electrodes or antennae. As a result, heat is generated by a modality-specific pathway. During RFA, the temperature rise is produced by a high frequency oscillating electrical current that induces resistive heating surrounding the radiofrequency electrode and tissue hyperthermia (Table 1) [8]. MWA occurs through the biophysics of dielectric hysteresis, which compels polar molecules (e.g. water) to instantly realign with the oscillating field, causing an increase of the kinetic energy of the molecules and hence tissue heating.

During RFA and MWA procedures, a 2—3-fold elevation (from 37 °C to ≥ 100 °C) of tissue temperatures is induced. Sustained exposure to such high temperatures cause cell death due to direct and indirect injury [9]. Direct damage affects the tissue that is closest to the application tip, which is exposed to temperatures of ≥ 50 °C. The heat causes protein denaturation and cell membrane dysfunction, which causes cells to undergo acute coagulative necrosis. Moreover, tissue desiccation and destruction of microvasculature also occurs as a result of elevated temperatures. At temperatures ≤ 45 °C, tissue injury is triggered by indirect pathways. Sublethal and reversible damage occurs at temperatures between 41 and 45 °C; cells that are exposed to these temperatures are more susceptible to injury and their metabolic functions might be negatively affected. Furthermore, the damaged tissue expresses vascular adhesion molecules and chemokines that activate the immune system [9]. At temperatures up to 41 °C, hyperemia occurs and the heat shock response is initiated [10,11].

Hypothermic ablation

Cryoablation systems use extreme cold (temperatures below −40 °C) to destroy tumor tissue by using needle based probes. The rapid tissue cooling can either be achieved by direct circulation of liquid nitrogen, or through the Joule—Thompson effect by using argon gas. The working mechanism of cryoablation is based on two principles:

- crystal formation;
- osmotic shock [12].

Intracellular crystal formation is a result of negative thermal expansion due to prompt tissue cooling, and leads to cell swelling and ultimately permanent cell membrane injury. Cells in the near vicinity of the cryoprobe are destroyed by this mechanism, whereas more peripherally located cells are susceptible to cell death induced by osmotic shock. During cryoablation, ice formation in the extracellular space leads to a hyperosmotic environment, which causes intracellular fluid outflow and cell dehydration. Oppositely, posttreatment-thawing causes osmotic stress by reversal of the osmotic gradient that subsequently initiates influx of extracellular fluid resulting in cell expansion and membrane rupture.

Table 1 Characteristics of the different ablation techniques.

	Ablation technique	Ablation effect	Treatment effect			
			Lung tumors	Liver tumors	Kidney tumors	Bone tumors
RFA	Application of a high-frequency oscillating electric field	Resistive heating surrounding the electrode tip and tissue hyperthermia	+++	+++	+++	+++
MWA	Application of a propagating electromagnetic energy	Tissue hyperthermia by dielectric hysteresis	+	+++	±	+ +
Cryoablation	Application of liquid nitrogen or argon gas	Crystal formation and osmotic shock	+ +	−	+++	+++
IRE	Application of electric pulses	Irreversible cell membrane disruption	±	+ +	±	±

RFA: radiofrequency ablation; MWA: microwave ablation; IRE: irreversible electroporation.