Image guided Ablation

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Published in:
Scottish Medical Journal

DOI:
10.1177/0036933020973637

Publication date:
2021

SCOTTISH MEDICAL JOURNAL

Editorial

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Scottish Medical Journal
2021, Vol. 66(4) 175–177

DOI: 10.1177/0036933020973637
journals.sagepub.com/home/scm

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Ablation refers to the local application of optical, acoustic or electrical energy and cold as to induce irreversible cell injury, apoptosis and coagulative necrosis of tissues. By contrast to surgical excision, ablation is a minimally invasive treatment option, whereby the scarified tissue remains *in situ* and is being absorbed over several months and transformed to a scar. Clinical use of ablation encompasses the treatment of various tumors, including liver, lung, kidney, pancreatic, head and neck cancer and bone metastasis. Additionally, neurological disorders, particularly essential tremor and Parkinson's disease, can be treated by ablation of brain tissue or neuronal structures.[1] Relatively novel is the use electrical energy in a certain pattern that induces cell apoptosis without coagulation, referred to irreversible electroporation (IRE), see Rui Chen et al. in this issue of *SMJ*. In order to decide which kind of local cell destruction is useful and can be applied safely a thorough understanding of the underlying principles is essential. In addition, it is required to use an appropriate imaging technology to monitor and control the process of tissue destruction.

The process of energy-induced cell/tissue destruction consists of two phases through direct and indirect mechanisms. The direct damage of cells occurs rapidly after exposure of the target tissue to high temperature, alteration of the cell membrane, dysfunction of mitochondrial and inhibition of DNA replication. Changes of cell membrane fluidity and permeability are considered as the major cause of cell injury, leading to dysfunction of actin filaments and microtubules and impairment of facilitated diffusion across the cell membrane.[2] Mitochondria are affected by high temperature, increasing leakage of protons through the inner mitochondrial membrane and changing the ultrastructure in minutes.[3] Besides the changes in cellular level, heat-induced denaturation of key replication enzymes DNA polymerase α and β, which is responsible for semiconservative DNA replication and DNA repair synthesis respectively, thereby inhibiting DNA replication.[4] Denaturation of polymerase substrate chromatin, abnormal condensation of non-histone nuclear matrix proteins, disruption of RNA synthesis and the release of lysosomal enzymes are believed the mechanisms of heat-mediated reproductive cell death.

The indirect mechanism occurs via several mechanisms, including induction of apoptosis, the release of cytokines and stimulation of immune response. Apoptosis is increased in the peripheral zone of the central ablated lesion, which undergoes coagulative necrosis. Expression of essential apoptotic protein p53 was upregulated and bcl-2 was downregulated in human liver cancer tissues after ablation treatment.[5] Release of pro-inflammatory cytokines such as interleukin-1β (IL-1β), IL-6, IL-8, IL-18 and tumor necrosis factor-α (TNF-α) increase in several hours to days after ablation maximize the anti-tumor response.[6] Heat shock proteins (HSPs) are a large family of stress-induced proteins and play a key role in cell survival and development. Recently, HSP70 attracts interest in research and is concerned as a biomarker and potential anti-tumor targets. Preclinical and clinical evidences indicate that the upregulation of HSP70 expression may stimulate anti-tumor immunity by inducing various immunological processes and regulation of multiple pathways including stress-activated kinases pathway JNK, extracellular signal-regulated kinases ERK and cell cycle inhibitor p21.[7,8]

Energy transmitted into target tumor lesion and induces local tumor destruction. According to the energy sources, the clinical techniques can be categorized as radiofrequency ablation (RFA), microwave ablation (MWA), laser ablation (LA), irreversible electroporation (IRE) and high-intensity focused ultrasound (HIFU/FUS). Each of the technologies shows strengths and weaknesses in the ablation of various tissues and organs.

Radiofrequency ablation (RFA) is the most accepted modality for tumor ablation using an electromagnetic energy source with frequencies at 200–1200 Hz

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1000-5000 Volt for generation of heat.[9] One or more radiofrequency electrodes can be placed by open surgery, laparoscopic surgery or percutaneously, under the guidance of ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI). RFA is considered a feasible option for treatment of unresectable tumors like primary hepato-cellular carcinoma other malignancies and metastatic lesions. RFA has proven to show a lower complication rate compared to surgical excision.[10] However, due to the delivery of heat, the heating zone is limited to a few millimeters surrounding the active electrode with the risk that tissue may become dehydrated and dessicated during treatment. The heat-sink effect is a well-known limitation of RFA, describes the phenomena when heat is absorbed by blood flow, dissipating the thermal effect and reduce treatment efficiency.[11] Immune responses is induced after RFA, increasing tumor cell recognition and tumor-specific T cells, thereby supporting tumor-free survival of the patients.

The mechanism of MWA is similar to RFA, cause rotation of water molecules in cells, induce frictional heating and consequently cause coagulative necrosis. MWA applicator (antenna) delivers electromagnetic microwaves above 900 MHz and has emerged as an alternative method to RFA.[9] In comparison to RFA, MWA generates a larger heating area (up to 2 cm away from antenna) and higher temperatures with shorter treatment duration, the tissue penetration is more uniform and heat-sink effect is less relevant.[12] From the biological perspective, WMA stimulates local inflammation and anti-tumor immunity to a lesser extend compared to other ablation techniques.[13]

LASER is another option for thermal ablation. It transports high energy light through a small flexible optical fiber (diameter 0.2–0.8 mm) into organs. The light absorbed by tissue is converted into heat. LA is superior to RFA and WMA in precision and treatment efficiency. Laser probes have the advantages of MR-compatibility, allowing for non-invasive MR-imaging guidance and temperature monitoring via MR-thermometry.[14] Nevertheless, the limited ablation area (1–2 cm^2) and accurate placement of laser applicators in tumor are the main challenges.

The term *irreversible electroporation* (IRE) describes the permeabilization of the lipid plasma membrane with high external direct and alternate current (DC/AC) pulsed electric fields.[15] The initial formation of pore on cell membrane reversible, increasing the uptake of drug or plasmid DNA when sufficient level of energy is applied, the changes of membrane permeability are permanent and irreversible.[16] Different from the other ablative techniques, IRE is a relatively new technique with non-thermal cell destruction mechanism, regards as an alternative for the tissues which are not suitable for thermal ablation, especially in cardiology. Only cell membrane is affected by IRE, regeneration of blood vessels and bile ducts post-treatment is possible. The first study of IRE on human was published in 2011 for ablation of liver tumor, clinical trials of IRE ablation for treatment of prostate and pancreas cancer are undergoing.[17] IRE also demonstrates good potential to overcome the thermal-related limitations and can be used to support chemotherapy, but the optimal physical parameters to obtain tissue-specific death remain unclear.

HIFU/FUS is an access free ablation technique and has got regulatory approval for ablation of uterine fibroids, prostate cancer, bone metastasis and treatment of essential tremor. Single or multi-element ultrasound transducer are positioned outside the body, ultrasound beams travel to the focus zone and generate heat in the target region. The temperature in the target can be elevated to 60–85°C in seconds, the tumor with large volume is treated by scanning the focal zone through the entire tumor in clinic.[18] Treatment planning and real-time visualization can be realized with ultrasound-imaging or MRI. HIFU/FUS is feasible for both thermal and mechanical ablation because the application of acoustic waves at high energy can cause acoustic cavitation and temporarily generate pore on cell membrane (so-called sonoporation).[19] The air or bones in the acoustic field may lead to scatter or absorption of acoustic interface and consequently result in incomplete destruction.

Image guidance and imaging follow-up post-ablation is essential for assessment of treatment outcomes. Various imaging modalities like B-mode sonography, contrast-enhanced US, MRI, PET-CT are available for rapid visualization and calculation of ablated area.[20,21] The stiffness of ablated tissue is crucial and correlated with pathologic changes. Shear-wave elastography (SWE) is a reliable solution to display the stiffness of tissue after ablation with RFA,[22] MWA, LA,[23] IRE[21] and HIFU ablation[24] qualitatively and quantitatively. Sailev et al. reported the potential of targeted manipulation of apoptotic pathways by using high Intensity focused ultrasound for cancer treatment.[25] Cheng et al. describe in this issues of SJM the use of SWE to visualize IRE generated lesions in an VX2 tumour animal model. According to their findings SWE provides tissue stiffness information of different IRE ablation satges as a non-invasive method. SWE has already shown a great potential for detection prostatic lesion (Nabi et al.)[26] In combination with energetic tissue destruction it may allow to combine diagnosis and therapy in a "one stop shop".

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