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Irreversible Electroporation in Hepatopancreaticobiliary Tumours

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Abstract

Hepatopancreaticobiliary tumours are often diagnosed at an advanced disease stage, in which encasement or invasion of local biliary or vascular structures has already occurred. Irreversible electroporation (IRE) is an image-guided tumour ablation technique that induces cell death by exposing the tumour to high-voltage electrical pulses. The cellular membrane is disrupted, while sparing the extracellular matrix of critical tubular structures. The preservation of tissue integrity makes IRE an attractive treatment option for tumours in the vicinity of vital structures such as splanchnic blood vessels and major bile ducts. This article reviews current data and discusses future trends of IRE for hepatopancreaticobiliary tumours.

Résumé

Les tumeurs hépato-bilio-pancréatiques sont souvent diagnostiquées à un stade avancé, alors que l'encerclement ou l'envahissement des structures biliaires ou vasculaires de la région a déjà eu lieu. L'électroporation irréversible, technique d'ablation tumorale guidée par imagerie, induit la mort cellulaire en exposant la tumeur à des impulsions électriques à haute tension. L'intervention perturbe la membrane cellulaire tout en laissant intacte la matrice extracellulaire des structures tubulaires critiques. Grâce à sa capacité de préservation de l'intégrité des tissus, l'électroporation irréversible est une option thérapeutique intéressante pour détruire les tumeurs situées à proximité des structures vitales, par exemple les vaisseaux sanguins splanchniques et les voies biliaires principales. Le présent article examine les données actuelles et aborde les tendances futures concernant le recours à l'électroporation irréversible dans le traitement des tumeurs hépato-bilio-pancréatiques.

Key Words: Irreversible electroporation; IRE; Pancreatic neoplasms; Liver neoplasms; Perihilar cholangiocarcinoma

Hepatopancreaticobiliary (HPB) tumours are typically and insidiously characterized by a lack of symptoms, preventing prompt diagnosis, and by rapid local progression, leading to encasement or invasion of local biliary and vascular structures. This precludes safe curative-intent surgery in the majority of patients with pancreaticobiliary tumours [1].

For early stage hepatocellular carcinoma and small colorectal liver metastases (CRLMs) thermal ablative therapies, such as radiofrequency ablation and microwave ablation, are nowadays widely accepted treatment options [2]. Nonetheless, thermal ablation is frequently contraindicated because of the risk of collateral damage to biliary, vascular or other heat-sensitive structures [2]. In addition, thermal ablation is less effective in proximity to major blood vessels because heat is lost to the flowing blood; a phenomenon known as the heat-sink effect [2].

The outcome of palliative chemotherapy or radiotherapy for pancreaticobiliary tumours remains highly unsatisfactory, with median overall survival (OS) rates of 6-10 months for locally advanced pancreatic cancer (LAPC) and 3-6 months for unresectable cholangiocarcinoma [3,4].

The paucity of effective treatment options has led to the search for new techniques to treat locally advanced disease.

A relatively novel ablation technique that holds promise for these difficult-to-reach tumours is irreversible electroporation (IRE). In contrast to other ablation techniques, the working mechanism of IRE is predominantly nonthermal [5]. It uses electric pulses to create nanopores in the cell membrane of the tumour cell, eventually causing the cell to undergo apoptosis [6]. As the effect of IRE is confined to the cell membrane, the surrounding extracellular matrix structures are unaffected [6].

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Indeed, the cellular constituents of surrounding and traversing structures such as vascular and biliary endothelial cells will be irreversibly damaged, similar to the target tissue. However, the preservation of the extracellular matrix constituting the structural and functional integrity of these vascular and biliary tubular structures, allows for fast tissue regeneration [6]. This makes IRE a theoretically safe treatment option for tumours in the vicinity of major bile ducts and splanchnic blood vessels.

Here we review the available clinical data and discuss future trends of IRE for HPB tumours that are not amenable for surgery or other ablation techniques due to their proximity to vascular, biliary, and intestinal structures. The general application of IRE will be described after which application for treatment of liver, pancreatic, and biliary tumours will be separately discussed.

Irreversible Electroporation

Working Mechanism

Depending on the magnitude of the electric field and its exposure time, pulsed electric fields (PEFs) provoke either temporary (reversible) permeabilization of cell membranes or permanent (irreversible) membrane disruption resulting in cell death [5]. The formation of temporary nanopores allows genes (electrogenotherapy) and drugs (electrochemotherapy) to transfer into cells that normally would not be able to penetrate the cell membrane. In clinical practice, the best known example of reversible electroporation is electrochemotherapy, such as injection of bleomycin before electroporation for the treatment of skin cancer [7].

When the PEFs exceed a certain threshold value ($\sim$650 V/cm) irreversible injury to the membranes of all cells within the ablation zone will lead to massive apoptosis that eventually evolves in fibrotic scar tissue at macroscopic level (IRE) [5].

Patient Selection

All patients should be discussed in a multidisciplinary team that, at least, consists of a diagnostic and interventional radiologist, an HPB surgeon, a medical and radiation oncologist, and a gastroenterologist. Patients should be evaluated in a preprocedural workup, including cardiac screening and full anesthetic review. Patients with poor functional reserve (American Society of Anesthesiologists score $>$3) should not be considered suitable candidates.

The increased cell membrane permeability caused by PEFs opens a path for ion transport, which can induce cardiac arrhythmias and defibrillation. In the milliseconds lasting time frame after cardiac contraction (ie, following the R-wave), the cardiac muscle is absolutely refractory to electrical stimuli. By synchronized pulse delivery within the refractory period of the heart, the risk of cardiac arrhythmias is reduced [8]. As the delivery of PEFs cannot be synchronized with cardiac R waves in patients with ventricular cardiac arrhythmias, this is considered an absolute contraindication for IRE. Although epilepsy is still listed as an absolute contraindication for IRE, the presumption that PEFs may evoke seizures by electrical discharges in the brain seems precipitated. Nielsen et al [9], who investigated signal alterations on electroencephalography during clinical IRE, did not find a reactive cerebral response after the delivery of high-voltage electric pulses. Transmucosal tumour invasion into surrounding intestines or extensive involvement of the duodenum should also be considered an absolute contraindication due to the increased risk of perforation or ulceration [10]. Other contraindications include congestive heart failure (New York Heart Association functional class $>$II), uncontrolled hypertension, and any implanted cardiac stimulation devices. Coronary artery disease (ie, myocardial infarction $<$6 months), atrial fibrillation, the presence of metallic foreign objects in the ablation zone (eg, nonremovable self-expanding metal biliary stent, and treatment with chemo- or immunotherapy within 4 weeks before the procedure are considered relative contraindications.

The NanoKnife System

Currently, the only commercially available IRE system is the NanoKnife (AngioDynamics, Latham, NY) (Figure 1). The system consists of a generator to which 6 monopolar 19-gauge probes can be connected. Furthermore, the AccuSync electrocardiogram-gating device (AccuSync Medical Research Corporation, Milford, CT) is connected to the generator and a 5-lead electrocardiogram, resulting in synchronized pulse delivery within the refractory period of the heart to prevent cardiac arrhythmias. The NanoKnife generator delivers electrical pulses through the active tips of the monopolar probes connected to the generator. The monopolar probes are 19-gauge needles, with an active tip that can be exposed between 0.5-4 cm with increments of 0.5 cm, depending on the depth of the lesion.

Procedure

Before the procedure, the exact size and geometric shape of the tumour is assessed to determine the number and configuration of the probes. Although a minimum of 2 probes is needed to create an ablation zone, multiple probes are often required to radically ablate the tumour including a tumour-free margin of at least 5 mm in all directions.

IRE needs to be performed under general anesthesia. Complete muscle relaxation is mandatory to counteract the stimulation of skeletal muscle due to the electrical pulses delivered and to prevent movement of probes secondary to muscle contraction [9]. Before pulse delivery, complete muscle relaxation should be confirmed by establishing a train-of-four ratio of 0 [9]. It is recommended to connect the patient to an external defibrillator to allow rapid intervention in case of ventricular arrhythmias.

IRE can be performed during open laparotomy using intraoperative ultrasound (US) or percutaneous using contrast-enhanced computed tomography (CECT) or US guidance. For the CT-guided approach, CT fluoroscopy is strongly recommended to allow dynamic and repetitive real-time visualization of the needle electrodes, the target lesion, and its