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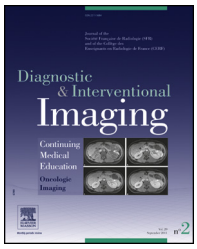

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Irreversible electroporation for locally advanced pancreatic cancer

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Abstract Pancreatic adenocarcinoma is one of the solid cancers associated with the poorest prognosis; the only curative treatment remains surgical resection but in most cases, this treatment is not possible because of distant metastasis or local extension. Irreversible electroporation is a new tumor ablation technique, which provides cellular apoptosis without any thermal coagulation effect. This technique helps preserve the ducts, vessels or nerves located in the treatment area. This article reviews the current knowledge regarding the use of electroporation for the treatment of pancreatic adenocarcinoma.

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Ninety-five percent of pancreatic cancers are adenocarcinomas. The diagnosis is still usually made at a late stage when the patient present abdominal pain, jaundice or deterioration in general health. Consequently, at the time of diagnosis, only 15% of patients have surgically resectable disease whereas 85% of patients have a locally advanced or metastatic disease and are therefore beyond the reach of surgery. For those patients who are not amenable to surgical resection, the 5-year-survival rate falls to less than 5%. For patients who can be operated, the 5-year-survival rate is around 20%.

Whilst everyone understands the concept of metastatic disease, locally advanced disease is more specific to the pancreas. Considering the retroperitoneal situation of the pancreatic gland, the tumor tends to spread quickly the superior mesenteric and/or hepatic artery and/or coeliac trunk and/or junction of the mesenteric and portal vessels. In this situation, the only treatment option is a combination of chemotherapy with gemcitabine or folfirinox, palliative surgery (biliary and gastric shunting) and/or radiotherapy.

In view of the limited treatment options, irreversible electroporation (IE) has recently been proposed to treat locally advanced pancreatic cancer [1]. IE has been around for over 30 years [2] when it was initially used to destroy microorganisms or introduce drugs into cells in in vitro cell cultures. It has more recently emerged as an effective method to destroy tissue [3]. Above all, however, IE can destroy cells located into a target area wherein collagen architecture of the vascular, biliary or neuronal structures is preserved. [4].

This article reviews the current knowledge about the use of electroporation to treat pancreatic adenocarcinoma.

Mechanisms of cell death from electroporation

IE uses very high voltage current, maximum 3,000 volts, delivered in microseconds (70 to 80 microsecs) pulses. These ultrashort electrical pulses create multiple microscopic holes within the cell membrane resulting in irreversible cell damage due to interference with homeostatic mechanisms [5]. Apoptosis does not occur immediately but only after a few days. The method is therefore completely different from thermal ablation techniques producing heat (radiofrequency or microwave) or cold (cryotherapy); indeed, IE does not cause coagulation necrosis [6,7]. A summary of the major differences between thermal and electroporation methods are shown in Table 1.

Histologically, early changes occur in the target tissue as early as 30 minutes although the macroscopic changes are slower. Normal tissue regenerates after several weeks and the collagen structures preserved by IE are used as ''guides'' for endothelial or duct cells restoring a normal ductal or vascular architecture over a few weeks. This has been clearly shown in a mouse model of pancreatic cancer [8] and confirmed on a pig model [9].

Practical aspects of treatment

The aim of treatment is to surround the tumor with two to six needles [10]. The number of needles chosen depends on the size and shape of the target lesion. The distance between each needle should not be over 2.5 cm and not under 1 cm and all of the needles must be positioned in parallel. It is occasionally difficult to correctly placed needles, which requires previous experience with ablation techniques, and if possible with multipolar techniques. A precise guidance method is also recommended and in our view, CT achieves this better than ultrasound although there are numerous descriptions of ultrasound guidance in the literature. The other purpose of guidance is to avoid puncturing at risk organs although a transgastric or transhepatic approach may be used as the needles are thin (22 Gauge). In terms of vascular structures, the manufacturer recommends the needle be positioned at least 2 mm away from large vessels in order to avoid any risk of damage and the risks of burns as it has been shown that the temperature may reach 62.8 °C in a radius of approximately 0.5 cm around the needle tip.

Treatment can be delivered in different approaches. Surgical groups commonly prefer a peroperative approach, which allows to check the peritoneal cavity and to exclude possible carcinomatosis. This approach also has the advantage of allowing the needles to be positioned parallel to the mesenteric vessel which is the best approach in cases of mesenteric involvement. A percutaneous approach has also been proposed, which has two major advantages of being less invasive and enabling CT guidance. By this way, correct needle positioning can cause real difficulties and it could be sometimes more difficult to position needles along the axis of the mesenteric vessels. It also does not allow a peritoneal cavity assessment.

All of the procedures need to be carried out under general anesthesia, synchronized with an electrocardiogram and under total muscle relaxation [11]. The size of the

Table 1 Main differences between thermal ablation methods and irreversible electroporation (IE).

Effects	Hyperthermia methods (RF and MW)	IE
Target tissue damage	Coagulation necrosis	Cell membrane
Protein damage	Yes	No
Connective tissue	Coagulation	No
Nerves and vessels	Coagulation	Theoretically not coagulated
Heat sink effect[a]	Variable	No

RF: radiofrequency; MW: microwave.
[a] The Heat sink effect describes a reduction in temperature due to vascular cooling (at 37 °C) in the treatment area, potentially reducing the effectiveness of treatment.

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