

## Possibilities of the method of irreversible electroporation in treatment of the local and widespread pancreatic cancer

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**Abstract.** Methods of a local destruction of tumors didn't find till today wide circulation in treatment of patients with formations of the pancreas (P). It is bound to features of blood supply, anatomical and histological structure of PZh, and also a large number of complications and a recurrence.

The technique of the irreversible electroporation (IE) represents a new unique method of not thermal ablation at which impact on tissues is carried out by short electric impulses of high voltage (to 3 kV) that involves irreversible rising of permeability of cellular membranes and death of cells. The optimum mechanism of rising of permeability of a cellular membrane electric impulses concerning their frequency or repetitions is yet not up to the end clear; it is recognized that outcomes depend on amplitude, duration and number of impulses. Influence has to be synchronized with a cordial rhythm in order to avoid development of an arrhythmia. Existence at the patient of an arrhythmia and the artificial driver of a rhythm is contraindication to carrying out an electroporation.

We have experience of use of a technique for 18 patients with a locally-spread pancreatic cancer. It was succeeded to reflect the main advantages of a new technique in our experience, such as comparative simplicity of workmanship, safety for vascular and pro-current structures, the minimum impact on function of a pancreas.

Efficiency of a destruction is proved to ultrasonic, computer and morphological researches in the postoperative period. The maximum term of observation made 19 months.

Though exact indications to use of NE still accurately aren't defined, the international experience and the first own data allow to state efficiency of new technology in palliative surgical treatment of perivascular tumors of a pancreas, and also its safety.

### 1. Introduction

Thirteen thousand people die of a pancreatic cancer in Russia annually. Among men mortality from pancreatic cancer — 10 out of 100 thousand men, and among women — 8,1 out of 100 thousand women. Statistically speaking, mortality of the population of Russia caused by new malignant growths, the relative frequency of a pancreatic cancer amongst men — 8,2% - 6th place; amongst women — 4,1% - 8th place. The pro-current adenocarcinoma of pancreas enters the top ten of the



most frequent causes of death by oncological diseases in Western Europe and America: 40 thousand deceased annually in Europe and 30 thousand in the USA [1]. The growth of pancreas cancer rate is noted in all countries where there is a high life expectancy rate and the so-called "western way" of living taken by the population. According to D.G.Haller [2], 40% of patients with pancreatic cancer to the time of diagnosis already have locally advanced common process, and only less than 20% of cases it is limited by the capsule of the gland. Early forms of pancreatic cancer are found in 3,8% of cases. Nevertheless, an important fact is that new malignant growths of pancreas in general are characterized by low sensitivity to medicinal therapy. However, productivity of some local ways of influence as interventional technologies with embolization of vessels of a tumor, local destruction applying the means of cryo-frequency, thermo-frequency and radio-frequency ablation, which force us to conduct an active research for new methods. The method of irreversible electroporation of tumors originates from a way of injecting cytotoxic substances into a tumorous tissue by means of reversible electroporation known as electrochemotherapy. The conducted research showed [3] that the characteristics of electric fields used at electroporation did not lead to a critical temperature increase ensuing the energy dispersion, which permits to find this data as a method of non-thermal ablation. Despite the medical technology of reversible electroporation used in the past 20 years, an interest in applying this technique has highly increased within the usage of irreversible electroporation. Likewise-reversible, at irreversible electroporation the powerful external electric field influences cells that leads to an increase in transmembrane potential and induces formation of pores in a membrane. Forming of a permeable pore becomes possible only on reaching the critical threshold level which depends on a type of cell and can usually be found in range from 200 to 300 mV/cm. The power of an impulse and its duration with exceeding the threshold level of stability of a cellular membrane leads to formation of multiple nano-pores. The nano-pores created in a membrane under the influence of electric field remains is constantly open. These changes conduct to a cellular death because of inability of a membrane to return to an initial homeostatic state.

Cells are densely compartmented by the bi-lipid plasma membranes, providing internal regulation - and extracellular transportation of solutes. When external electric field influences a cell, it spreads around a cell and not directly through it. It creates a difference in flow density on a surface of a cell and inside, and leads to an onset of potential difference on the surface of membrane. When transmembrane's potential reaches a certain critical level, the cell becomes unstable and plasmatic membrane is subject to destruction or restructuring with the formation of the nano-pores, providing a passive incoming ionic flow. Because of the membrane becoming permeable, there is an increase of energy demands for maintenance of trans-membrane's difference for concentration of ions cellular increase. Conductivity of a plasmatic membrane sharply increases and, if ATP-dependent ionic pumps are incapable of compensating diffusion of ions through pores in a plasmatic membrane, power malnutrition and termination of biochemical processes take place, the so-called "biochemical arrest" which leads to the death of a cell. Irreversibly-damaged cells are eliminated by immune system. Several authors showed that ultrashort (more than a 100 in a nano-second) and high-intensity (200-300 sc) impulses influence directly the intracellular organelles without causing an irreversible damage to cellular membranes. The cellular death is caused in this case by the apoptosis induced by mitochondrions and connected to the release of calcium from a cytoplasmic reticulum, and the damage of DNA [4,5].

Precision mechanisms of a cellular death at NE are still subject to a debate. However, it is considered that both mechanisms necrosis and apoptosis can play a role in cellular destruction. The latest data indicates an increase of markers of apoptosis in the zone of tissue that has undergone NE. Apoptosis initiates inborn cellular regeneration, thus less time for recovery of tissue is required, than by means of necrosis. Moreover, at apoptosis fibrous changes are found to a lesser extent in areas undergone ablation than at a necrosis which prevents further damage of organs which have undergone ablation, and that is confirmed by data of conducted research.

## 2. Materials and methods

Patient A., 56 years old, has been hospitalized to the surgery department of FNKTs on April 11, 2013, complaining at the continuous pains in the epigastric area increasing after consuming food, mouth dryness, nausea, weigh-loss, weakness. From the anamnesis, it is known that since March 2012, there have been signs of weakness and fast fatigue. Since April 2012 pains in epigastric area with back irradiation, air regurgitation, vomiting after consumed food began to disturb. An x-ray examination of a stomach performed on 24.04.2012 - depot of barium in peripyloric department of stomach. Throughout May 2012 the specified symptoms remained with a growing tendency. Pains became constant. Patient has undergone treatment on an outpatient basis and in hospital with no visible effect. At EGDS from 17.05.2012-a massive ulcer of subcardial department of a stomach. A biopsy - data for neoplastic process of stomach has not been obtained. On the other hand, the carried-out therapy has reached a positive effect. EGDS of 14.06.2012 - an ulcer of an upper part of a third of a stomach is in a stage of full scarring. EGDS of 20.07.2012: diffusion gastritis. Symptoms of chronic pancreatitis. Retrogression since January 2013 when pains in epigastric area renewed, 03.03.2013 noted vomiting with coffee-ground. In emergency, patient hospitalized to the surgery ward of a local hospital. At EGDS - the ulcer of a bulb in a range from 0,4-0,5 cm covered in fibrin, hemosiderin. Esophagitis. Haemostatic, infusion, anti-ulcerous therapy has been carried out. EGDS from.14.03.13 - hypostasis, a bulb hyperemia, punctate bleeding noted. Patient discharged from hospital on an out-patient stage of treatment. Due to the continuous pain syndrome in the upper parts of the stomach, patient hospitalized for inspection and treatment at the department of gastroenterology of FNKTs of FMBA of Russia. 10.04.2013 of ultrasonography of inards. Conclusion. Liver is condensed, is diffusively-changed. The pancreas has enlarged (head 3,9x4,5; body 1,9; tail 2,4 see), focal education in a pancreas head projection, 3,9kh2,7sm cystous and solid structure, in other departments a parenchyma diffusively heterogeneous, echogenicity is reduced. Virsungov Canal is expanded to 0,4 cm in a body. A bilious bubble banner in the neck and body, and dense walls.

By the results of video-esophagogastroduodenoscopy from 11.04.2013. There is an apparent infiltration of a mucous membrane of a post-bulbar department. A bulb of a duodenum is of normal form, starting from the distal part of a bulb in the post-bulbar department and up to the level of a big duodenal nipple a mucous membrane is apparently hyperemic, edematous a gleam circumferentially is narrowed to 0,9 cm. The compensated circular stenosis of a gleam of a duodenum. The biopsy/cytology is executed.

11.04.2013 KT of abdominal organs with a contrast agent: The liver has not increased in its size, intrahepatic bile ducts has not expanded. Porta is differentiated. The portal vein has not expanded. Vascular drawing is not deformed. Holedokh is not expanded.

The pancreas is positioned as usual, body and tail without visible anomalies. The head is visualized in the form of a conglomerate with the descending part of a duodenum surface of which is maleficiated. The conglomerate is intimately adhering to the frontal wall of the lower vena cava, flattening its gleam at this level, to the frontal surface of the right kidney, to a medial contour of the liver, to the renal leg. Contours of the conglomerate are indistinct with a local infiltration surrounding fatty tissue, undergoing contrasting strengthening, there is a noted active erratic conglomeration of it. Virsungov Canal is not expanded, in structure of education is not traced. The celiac trunk, the general hepatic artery and splenic arteries are traced without signs of involvement in process.

24.04.2013 under an endotracheal anesthesia an operative measure is being executed: Laparotomy. An irreversible electroporation of tumor of the head of pancreas - the "Nano-Knife" system, under intraoperative ultrasonic targeting. The upper median laparotomy has been carried out. In an abdominal cavity, the ascetic exudate up to 500 ml, it's taken for cytology testing. Audit of an abdominal cavity is carried out. In a liver, on innards without focal pathology. Tissue of liver of grayish color, condensed. There is no carcinomatous of a peritoneum. Retroperitoneal and regional lymph nodes are not enlarged. The pancreas' head is hilly, dense and has increased to 5 cm in the diameter. The stomach is mobile. Mobilization of a pancreatoduodenal complex by the method of Kokher. It has been found that there is a pancreas head tumor with involvement of a uniform conglomerate duodenum, it is intimately soldered from the lower vena cava to 3x3,0\*3 cm.

Considering the findings, the decision is to limit the operation's volume to cytoreductive, and to execute a tumor electroporation under ultrasonography control has been carried out. The tumor biopsy by the biopsy gun - 1 fragment to 0.6sm is taken, material is sent for planned histologic research. Fabric bleeding is noted. For hemostasis in the tumor i.e. a bleeding part the device, RITA Habib 4 x Kit REF 4401 is inserted, the hemostasis is carried out. Further 4 monopolar electrodes of the "Nano-Knife" system at the distance of 1.5 cm are inserted into the tumor, irreversible electroporation of the tumor in the mode of 80 impulses at 70 microseconds, with a current of 30 amperes, time of exposure - 8 minutes is carried out. Essential changes to the characteristics in homeostasis after electroporation are noted. A vital distinctive feature of the technique is that for the set tumor measurements the software itself defines the mode and time of exposure considering the quantity of electrodes.

### **3. Results**

The current of the after-surgery period on the 7<sup>th</sup> night has been complicated by development of acute pancreatitis, a focal pancreatectomy. The diagnostic laparoscopy, sanitation and drainage of an abdominal cavity concerning the existence of an exudate in a free abdominal cavity was carried out. Conservative infusion, antibacterial, anti-secretory, analgesic therapy, nutritive support, prevention of thromboembolic complications were carried out. Against the carried-out treatment - positive dynamics in the form of subjective improvement of health, reduction of pain syndrome, permanent decrease in the level of pancreatic amylase of blood, decrease in a leukocytosis, according to tool inspections there is absence of liquid accumulations in peripancreatic cellulose. Patient released in a satisfactory condition for the continuation of treatment on an out-patient stage.

Terms of supervision for this patient make-up 7 months as of today. Since the follow-up examination in November, 2013. Based on ultrasonic, an X-ray, computer and magnetic-resonant inspections, data has not been received for the recurrence of the disease.

### **4. Discussion**

One of the unique characteristics of NE that distinguishes it from other types of ablation - is a lack of damage of tubular structures (arteries, veins, channels) and nerves. For other types of ablation of tumors, such structures are completely obliterated under the influence of the extreme temperatures leading to protein denaturation in an ablation zone. Thus, thermal ablation leads to non-selective destruction of proteins and DNA, thus at NE the cellular death is caused by the apoptosis induced by the formation of the multiple pores in a membrane as mention above. At the same time, the formations created by mainly elastic, collagen structures and proteins of a paracellular matrix are not exposed to damage at NE [6].

The main restriction for the efficient monitoring of hyper thermal as of cold types of ablation, is the long-time supervision necessary for an assessment of an effectiveness of the carried-out therapy. Following the experiments, it is shown that damage caused by NE quickly allowed with the minimal hem in approximately two weeks' time [9]. Most likely, it can be explained by preserving of the micro vessels up to the level of arterioles in all areas of influence of electric field at NE while cryo-and radio-frequency ablation of educations leads to almost full revascularization of a zone of influence and the subsequent long recovery of a microvascular bed from edges of a zone of a necrosis deep into tissues that increase terms of the formation of the devitalized tissue and reparation in the field of thermal influence [10]. The profile of safety of the technique of NE allows to use it widely at various localizations of tumorous processes [11,12].

### **5. Conclusion**

The experiment on the use of NE of a tumor of a pancreas has shown primarily the main advantages of a new technique which are expressed in the minimum invasiveness of intervention on the volume of operational reception, technical simplicity of execution in difficult zones in the anatomic relation, by satisfactory immediate results of a recurrence-free survival. The important characteristic is the safety of NE for pro-current structures and vascular educations provided as at a stage of introduction of

electrodes of UZI/KT with targeting, and the direct effects of electroporation concerning tissues of components of the specified structures. This method of ablation and a possibility of its repeated usage for one patient will allow to expand volumes of assistance to initially irresectable patients with pancreas' tumors. A more in-depth indication to the application of this method and frequency rates of its use is in demand of further research.

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