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CLINICAL CASE REPORTS

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REPEATED IRREVERSIBLE ELECTROPORATION IN A LOCALLY ADVANCED PANCREATIC CANCER

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Abstract

It is reasonable to consider the technical possibility and oncological feasibility of the local tumor destruction in patients with locally advanced pancreatic cancer (PCa). Irreversible electroporation (IRE) is a non-thermal method of local tumor ablation, which uses non-thermal energy of high-voltage ultrashort electric fields localized between electrodes to create nanopores in the cellular wall with the following cellular death. The zone of impact can be accurately predicted using the location of the electrodes. A fairly clear and controlled ablation boundary without a clinically significant zone of perifocal tissue damage reduces the risk of accidental injury to the wall of a hollow organ. The method is based on a change in the permeability of the cell membrane and the development of apoptosis, which allows to act directly on the ducts and the great vessels infiltrated by the tumor without a high risk of damage. The presented case shows that IRE is advisable to use as a part of the combined treatment of patients with locally advanced PCa. There were no complications observed after the IRE. Radiological evaluations and pathologic reports showed an adequate long-term local control. Also, good results were obtained in the overall life expectancy, given that we are talking about unresectable ductal adenocarcinoma of the pancreas. The patient passed away in 39 months from the beginning of the treatment and in 26 months from the initial IRE. In case of local relapse, repeated electroporation with a good long-term result is also possible. The time to progression exceeded eleven months after electroporation performed for a local relapse. According to magnetic resonance imaging, both locoregional relapse and distant liver metastases were detected. The patient lived 16 months after a repeated IRE session and died of pulmonary embolism on the background of chemotherapy.
Favorable prognostic factors are the presence of an objective response to previous conservative treatment, compliance with the parameters of electroporation, complete inclusion of tumor infiltration in the affected area.

Keywords:
unresectable non-metastatic pancreatic cancer, ductal adenocarcinoma, local relapse of pancreatic cancer, irreversible electroporation, combined treatment for pancreatic cancer

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КЛИНИЧЕСКОЕ НАБЛЮДЕНИЕ

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СЛУЧАЙ ПОВТОРНОГО ПРИМЕНЕНИЯ НЕОБРАТИМОЙ ЭЛЕКТРОПОРАЦИИ ПРИ МЕСТНОРАСПРОСТРАНЕННОМ РАКЕ ПОДЖЕЛУДОЧНОЙ ЖЕЛЕЗЫ

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Резюме

При местнораспространенном нерезектабельном раке поджелудочной железы (РПЖ) целесообразно рассмотреть техническую возможность и онкологическую обоснованность локальной деструкции опухоли. Необратимая электропорация (НЭП) – нетермический метод локальной абляции опухоли, зону воздействия которого можно контролировать расположением электродов. Под воздействием нетепловой энергии высоковольтных ультракоротких электрических полей, локализованных между электродами, в клеточной оболочке образуются постоянные нанопоры, что приводит к нарушению клеточного гомеостаза и гибели клетки. Достаточно четкая и контролируемая граница абляции без клинически значимой зоны перифокального повреждения тканей снижает риск случайного воздействия на окружающие органы и структуры, в первую очередь – стенку полого органа. Метод основан на изменении проницаемости клеточной мембраны и развитии апоптоза, что позволяет воздействовать непосредственно на инфильтрированные опухолью протоки и магистральные сосуды без высокого риска их повреждения. Представленный случай показывает, что НЭП целесообразно использовать в плане комбинированного лечения больных местнораспространенном РПЖ. Не отмечено осложнений ни после первого, ни после второго сеансов НЭП. Методы лучевой диагностики, а также морфологические исследования показали возможность адекватного локального контроля. Также получены неплохие результаты в общей продолжительности жизни, учитывая, что речь идет о нерезектабельной протоковой аденокарциноме поджелудочной железы. Больная прожила 39 месяцев от начала лечения и 26 месяцев от первого сеанса НЭП. В случае местного рецидива также возможна повторная электропорация с хорошим отдаленным результатом. Время до прогрессирования превысило одиннадцать месяцев после электропорации, выполненной по поводу локального рецидива. По данным магнитно-резонансной томографии выявлен как локорегионарный рецидив, так и отдаленные метастазы в печени. Пациентка прожила 16 месяцев после повторного сеанса НЭП и умерла от тромбоэмболии легочной артерии на фоне начатой химиотерапии.
Благоприятными прогностическими факторами являются наличие объективного ответа на предшествующее консервативное лечение, соблюдение параметров электропорации, полное включение опухолевой инфильтрации в зону воздействия.

Ключевые слова:
нерезектабельный неметастатический рак поджелудочной железы, протоковая аденокарцинома, локальный рецидив рака поджелудочной железы, необратимая электропорация, комбинированное лечение рака поджелудочной железы

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INTRODUCTION

Worldwide in 2018, advanced pancreatic cancer (PCa) was diagnosed in 460,000 cases, and 432,000 patients with this disease have died [1]. PCa is discovered at the time when radical surgical resection is possible in 10–20 % of cases; on the other hand, 30–50 % patients have distant metastases [2; 3]. Local destruction methods can be applied when diagnosis of locally advanced pancreatic cancer is determined (remaining 30–50 % of all cases) [2; 3]. When accurately applied, irreversible electroporation (IRE) differs favorably from other local destruction methods. Possibility to create an exact, easily controlled impact zone without any clinically proven thermal damage explains effectiveness and safety of this technique in case of use in close diligence of hollow organs, mainline vessel and/or bile/pancreatic duct infiltration [4]. It is possible to combine IRE with pancreatic resection [5]. It is advisable also to combine IRE with other treatment methods according to aggressive type of the disease progression [6].

The purpose of the study is to show the possibility and feasibility of repeated irreversible electroporation in selected patients with locally advanced pancreatic cancer as part of a combined treatment.

CASE REPORT

Patient V, a 68-year-old woman, complained on epigastric pain irradiating backwards. During initial MRI (02/12/2016), a solid lesion in pancreatic body had been determined. The lesion was 56 × 37 mm in size. Tumor markers level: CEA = 178 ng/ml, CA-19–9 = 152 U/ml. On 03/17/2016, the patient went through an exploratory laparotomy: a tumor nearly 60 mm in diameter infiltrated the common hepatic and the splenic arteries. The case was recognized as non-respectable, tumor biopsy was performed. Histology showed the presence of fibrous tissue fragments with ductal adenocarcinoma complexes. From March till June 2016 the patient underwent 5 cycles of FOLFIRINOX chemotherapy with neutropenia of grade II and thrombocytopenia of grade I as adverse effects.

Control CT-scan from 07/27/2016 showed a lesion in pancreatic body (57 × 38 mm), closely adjacent to the superior mesenteric artery and invading the common hepatic and the splenic arteries and the celiac trunk. Initial PET-CT with 18F-fluorodesoxiglucose (18F-FDG) scan data from 07/18/2016 revealed a lesion in pancreatic body (64 × 39 mm), SUV 3.22, no metastases were found.

Then a stereotaxic radiotherapy course was performed: five sessions between 08/03/2016 and 08/09/2016 using daily fraction dose of 7.5 Gy (total dose 37.5 Gy) with no complications noted.

Control MRI scan data from 09/13/2016 revealed stable disease with small reduction of tumor size to 51 × 35 mm. On control MRI scan data from 03/02/2017 a lesion (51 × 35 mm) in pancreatic body was observed–stabilization compared to 09/13/2016. General vessels were still invaded, however now it seemed possible to perform resection of the pancreas with resection of the celiac trunk. Tumor marker levels were CEA = 14.9 ng/ml, CA199 = 59.0 U/ml.

On 04/04/2017, we used laparotomic approach

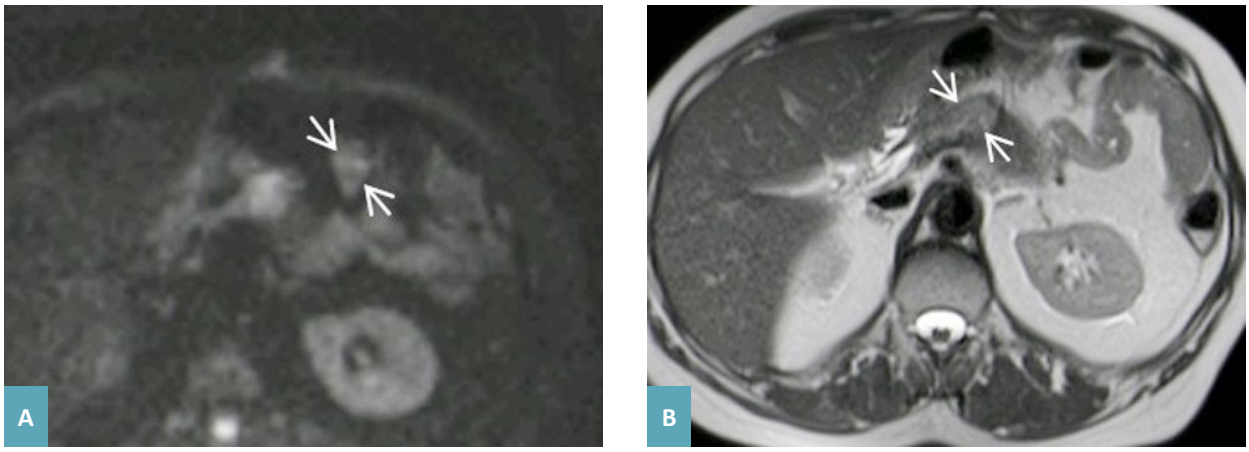

Fig. 1. Abdominal MRI dated 10/31/2017. Condition after electroporation. Proximal to the electroporation zone in the isthmus of the pancreas, a volumetric mass of up to 14 mm became apparent that is suspicious of local recurrence or continued growth, which is most clearly visualized with diffuse-weighted imaging (fig. 1A) and in the T2 mode (fig. 1B) – white arrows.

Рис. 1. Абдоминальное МРТ 31.10.2017 г. Состояние после электропорации. Проксимальнее зоны электропорации в перешейке поджелудочной железы обнаружена объемная масса размером до 14 мм, что вызывает подозрение на локальный рецидив или продолжающийся рост, который наиболее четко визуализируется при диффузно-взвешенной визуализации (фиг. 1А) и в режиме Т2 (рис. 1В) – белые стрелки.

and revealed the tumor in pancreatic body spreading to isthmus and tail. The tumor was 65 × 35 × 20 mm in size and invaded the mesentery root, the celiac trunk and the superior mesenteric artery. Thus the case was recognized as non-respectable. There were no signs of tumor generalization so intraoperative IRE was performed under ultrasound guidance. Number of electrodes used was 4, the length of active electrode pole, 20 mm, voltage, 1500–2500V, current, 30–45A, the number of impulses between each electrode pair in effective mode – 80, impulse duration – 90 microseconds. Large tumor size didn't allow to perform a single IRE-procedure, thus the tumor had been processed consequently from 5 locations. The technical parameters of IRE were observed, the repeated exposures were not required. Impact zone appeared to be 70 × 40 × 20 mm which covered the infiltration region completely. Blood loss was 250 ml, whole operation time was 390 min. There were no complications.

The control MRI data from 05/05/2017 (1 month later) and 07/05/2017 (3 months later) showed no signs of progression. Tumor markers level from 07/03/2017: CEA = 3.9 ng/ml, CA19–9 = 33.1 U/ml.

Control MRI data from 10/31/2017 (6 months following IRE) demonstrated the IRE impact zone size stabilization (42 × 31 mm) with no contrast enhancement in it. However, at the same time a new lesion (14 mm in diameter) in the pancreatic isthmus region had been detected close to the IRE impact zone which was highly suspicious to be a local relapse or a continued growth focus (fig. 1).

Control PET-CT with 18F-FDG data from 11/21/2017 also revealed two types of lesions in pancreatic body and isthmic region: 1) avascular IRE impact zone – 51 × 35 mm with SUV = 1.8 (compared to initial 64 × 39 mm and SUV 3.2 respectively); 2) lesion proximal to IRE impact zone 12 mm in diameter with SUV = 4.07 which was evaluated as a local relapse. There was no sign of distant metastases. Tumor markers level from 11/27/2017: CEA = 7.6 ng/ml, CA199 = 75.9 U/ml.

Considering radiological data on the local relapse in the isthmic region of the pancreas with no sign of distant metastases, we decided to repeat IRE as a local destruction technique. On 12/13/2017, a laparotomy and an intraoperative ultrasound examination were performed. A lesion (15 × 15 × 13 mm) was revealed in the isthmic region proximal to the initial IRE impact zone which was highly suspicious to be a local relapse (fig. 2).

A biopsy sample taken from this lesion showed adenocarcinoma cells (fig. 3).

The absence of malignancy in the initial IRE impact zone was also morphologically proven (fig. 4 and fig. 5).

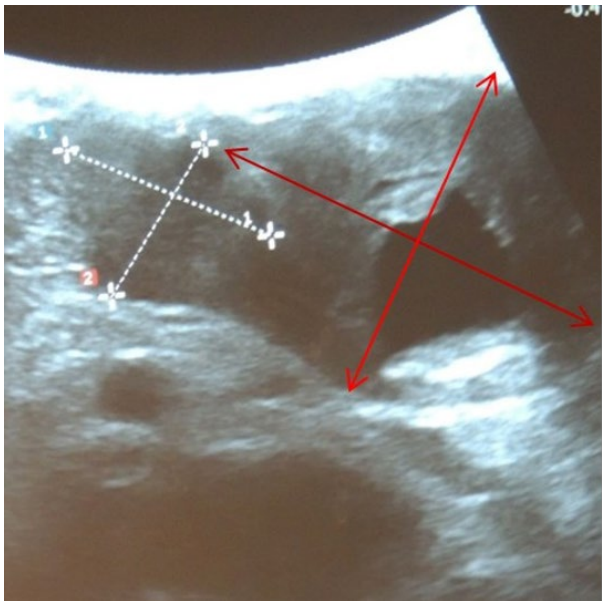

Fig. 2. Intraoperative data obtained during the second electroporation session. Data from intraoperative ultrasound – the area of the previous electroporation up to 5 cm – marked with red arrows, and next to it, the area of recurrence up to 1.5 cm, the boundaries are marked with a dashed line.

Рис. 2. Интраоперационные данные, полученные во время второго сеанса электропорации. Данные интраоперационного УЗИ – область предыдущей электропорации до 5 см – отмечены красными стрелками, а рядом с ней область рецидива до 1,5 см, границы отмечены пунктиром.

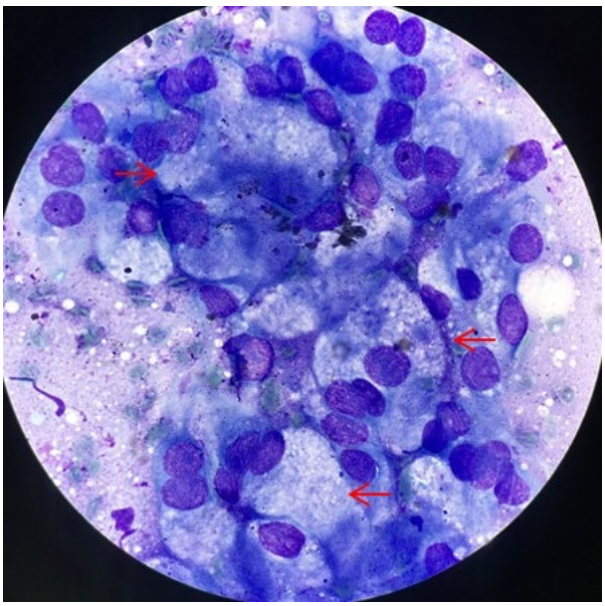

Fig. 3. Cytological data that confirms recurrence in the proximal direction from the area of the previous IEP session. Micrograph of the preparation, stained with azure-eosin, × 1000. Adenocarcinoma cells cover the visual field (marked with red arrows).

Рис. 3. Цитологические данные, подтверждающие рецидив в проксимальном направлении от области предыдущего сеанса НЭП. Микрофотография препарата, окрашенного лазурно-эозином, Ув. × 1000. Клетки аденокарциномы покрывают поле зрения (отмечены красными стрелками).

The secondary IRE of the local relapse zone was performed using four electrodes from two points of access. The length of electrode poles was 15 mm, initial voltage – 3000V, current – 34–42A, impulse duration – 80–90 microseconds, the number of effective impulses between each electrode pair – 80. The impact zone of secondary IRE appeared to be 25 × 20 × 18 mm completely covering the registered relapse zone. Blood loss recorded at 200 ml, whole operation time – 280 min. There were no complications.

Control MRI scan data from 01/15/2018 showed no signs of tumor progression with a haematoma 20 mm in diameter in the secondary IRE impact zone. Tumor markers level as of 01/13/2018: CEA = 6.2 ng/ml, CA199 = 110.9 U/ml. Between January and August 2018, eight GEMCAP chemotherapy courses were performed. There were neutropenia of grade II and thrombocytopenia of grade II observed in between. Control MRI scan data from 11/20/2018 (32 months since the start of chemotherapy, 19 months after the first and 11 months after the second IRE procedure) demonstrated a stabilization of the size of the initial IRE impact zone – 41 × 32 mm with no contrast enhancement. In the secondary IRE impact zone there was a fibrous tissue revealed in place of the previously described haematoma. There were no signs of tumor progression. Tumor markers level from 11/16/2018: CEA = 11.2 ng/ml, CA199 = 157 U/ml.

CT-scan 02/12/2019 revealed a lesion 55 × 34 mm in the area of previous IRE. In addition a tumor infiltration of the celiac trunk and the superior mesenteric vein was found. Distant metastases occurred in liver 3–15 mm in diameter. The patient has started chemotherapy (03/01/2019). She passed away due to the thromboembolism (June, 2019).

DISCUSSION

Only 10–20 % of patients with ductal PCa can go through curative resection, the median survival rate reaches 27 month and the 2-year local relapse risk is estimated as 60 % [2, 3]. In 30–50 % of cases, distant metastases were revealed at the moment when the diagnosis had been determined [2; 3]. Patients with metastatic PCa are generally managed by systemic

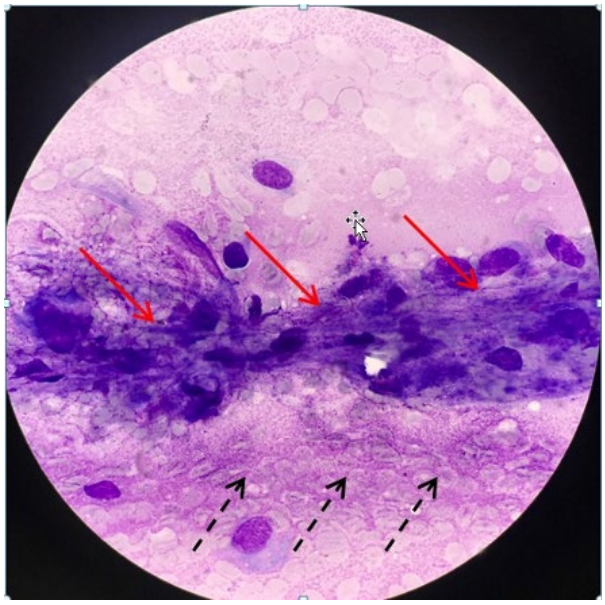

Fig. 4. Cytological confirmation of complete therapeutic pathomorphosis in the area of the previous IRE session. Micrograph of the preparation, stained with azure-eosin, × 1000. Structureless substance (black dashed arrows) and fibroblasts (red arrows).

Рис. 4. Цитологическое подтверждение полного терапевтического патоморфоза в области с предыдущего сеанса НЭП. Микрофотография препарата, окрашенного азур-эозином, Ув. × 1000. Бесструктурное вещество (черные пунктирные стрелки) и фибробласты (красные стрелки).

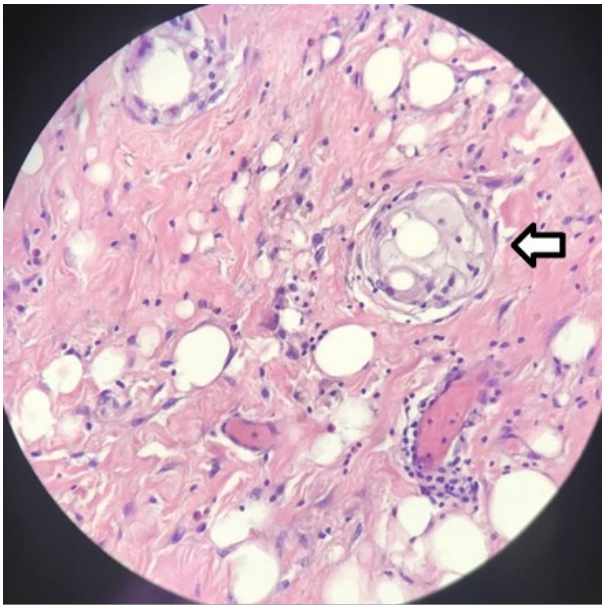

Fig. 5. Histological confirmation of the absence of a tumor in the area of the previously performed IRE. Micrograph of the preparation, stained with hematoxylin and eosin, × 400, a fragment of connective and adipose tissue, with lymphoid infiltration, xanthoma cells with lipogranuloma formation (indicated by an arrow), without elements of tumor growth.

Рис. 5. Гистологическое подтверждение отсутствия опухоли в области ранее выполненного НЭП. Микрофотография препарата, окрашенного гематоксилином и эозином, Ув. × 400, фрагмент соединительной и жировой ткани, с лимфоидной инфильтрацией, клетки ксантомы с образованием липогранулемы (обозначены стрелкой), без элементов опухолевого роста.

chemotherapy [7–9]. In the last group of patients (30–50 %), the tumor was diagnosed to be vastly locally advanced what approves impossibility of radical surgery because of the infiltration of major vessels. This group of patients is generally managed by systemic chemotherapy as the first step. According to meta-analysis the median survival rate of patients with locally advanced PCa ranged between 9 and 14.4 months in gemcitabin+nab-paclitaxel group vs 9–15.9 months in FOLFIRINOX group [9]. A large study LAP-07 showed that addition of radiotherapy following gemcitabine-based chemotherapy didn't improve the long-term results of patients with locally advanced disease (HR = 1.03, 95 % CI = 0.79–1.34, p = 0.83) [10]. If partial response or stable disease is achieved but the tumor is still unresectable local destruction methods are being investigated nowdays [2; 3].

The use of thermal-based methods of local destruction in case of pancreatic tumors was frequently limited because of close interaction with perifocal mainline vessels and hollow organs and absence of a clear and easily controlled border between the impact zone and the surrounding tissues. The required temperature regimen in the ablation region may be failed to achieve due to wide temperature variations caused by close location of perifocal mainline vessels, what in its turn decreases ablation quality. On the one hand, these facts can explain the difficulties in complete tumor ablation, on the other hand, the high risk of developing severe complications (hollow organ perforation, pancreatitis, acute stomach ulcers, bleeding, pancreatic- and/or bile-fistulas, bile ducts stricture formation, etc). D. A. Ionkin et al. reported a series of pancreatic tumors cryoablation with the complication rate 38.8 %. However the median overall survival rate of 18 month was reported [11].

Irreversible electroporation (IRE) is a relatively new method of local tumor destruction. In this case non-thermal energy of microsecond pulses of high voltage between electrodes are used to cause constant nanopores in cell wall which result in a change of permeability of the cell membrane, damage of intracellular homeostasis and apoptosis initiation. Thermal impact is absent in the general tissue mass subjected to electroporation and can be seen just within the electrode placement area causing coagulation necrosis without clinically significant perifocal swelling. It is possible to combine palliative pancreatic resection with IRE for residual tumor tissue [5].

Absence of a clinically significant thermal effect, clearly isolated tissue damage without a sufficient impact on stroma and possibility to create a well-controlled impact zone by electrode location make IRE a promising technique for the patients with PCa in cases when surgical resection or other ablation-based methods are not justified [12].

R. C. Martin and colleagues reported the largest experience of IRE in pancreatic cancer. The level of complications after IRE for locally advanced pancreatic tumors consisted 37 %, with the mortality rate of 1.5 %. The median survival rate for patients who received IRE appeared to be 18 month (24.9 month from the beginning of treatment), combined with palliative resection – 23 month (28.3 month from the beginning of treatment) [5]. The authors showed the possibility to use a less invasive transcutaneous approach besides laparotomy, making usage of the IRE technique more attractive [13].

Our case report clearly demonstrates the effectiveness of the combined approach to treatment of the patients with locally advanced pancreatic cancer using IRE. There were no complications observed either after the initial or after IRE for local relapse, which can partly prove the safety of this technique being applied in such difficult clinical case. Radiological evaluations and pathologic complete response leave no doubt in usefulness of IRE in spite of appearance of continued growth focus proximal to the initial impact zone. The patient passed away in 39 months from the beginning of treatment, in 26 months from the initial IRE, in 16 months after IRE of local relapse. Our experience let us assume that IRE should be applied for locally advanced PCa if tumor is not progressive after chemotherapy and complete coverage of tumor can be achieved. Accurate technique parameters compliance is necessary. IRE can be safely repeated in a case of local relapse or continued growth and no sign of distant metastases.

CONCLUSION

Literature data, as well as our case report, suggest that the addition of IRE to standard therapy for unresectable non-metastatic PCa may be justified in a selected group of patients. An indication for IRE may also be tumor recurrence after a previous electroporation.

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